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Authors
Labin, Jonathan E
Saggar, Rajan
Yang, Eric H
et al.

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INTERVENTIONAL ROUNDS

Left main coronary artery compression in pulmonary hypertension

Jonathan E. Labin MD[1] | Rajan Saggar MD[2] | Eric H. Yang MD[3] | Gentian Lluri MD, PhD[3] | David Sayah MD, PhD[2] | Richard Channick MD[2] | Abbas Ardehali MD[4] | Olcay Aksoy MD[3] | Rushi V. Parikh MD[3]

[1]Department of Medicine, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, California

[2]Division of Pulmonary and Critical Care, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, California

[3]Division of Cardiology, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, California

[4]Division of Cardiothoracic Surgery, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, California

Correspondence
Rushi V. Parikh, Assistant Clinical Professor, Division of Cardiology, University of California, Los Angeles, 100 Medical Plaza, Suite 630 West, Los Angeles, CA 90095, USA.
Email: rparikh@mednet.ucla.edu

Abstract

Extrinsic compression of the left main coronary artery (LMCA) by a dilated pulmonary artery (PA) in the setting of pulmonary arterial hypertension (PAH) is an increasingly recognized disease entity. LMCA compression has been associated with angina, arrhythmia, heart failure, and sudden cardiac death in patients with PAH. Recent studies suggest that at least 6% of patients with PAH have significant LMCA compression. Screening for LMCA compression can be achieved with computed coronary tomography angiography, with a particular emphasis on assessment of PA size and any associated downward displacement and reduced takeoff angle of the LMCA. Indeed, evidence of a dilated PA (>40 mm), a reduced LMCA takeoff angle (<60°), and/or LMCA stenosis on CCTA imaging should prompt further diagnostic evaluation. Coronary angiography in conjunction with intravascular imaging has proven effective in diagnosing LMCA compression and guiding subsequent treatment. While optimal medical therapy and surgical correction remain in the clinician's arsenal, percutaneous coronary intervention has emerged as an effective treatment for LMCA compression. Given the prevalence of LMCA compression, its associated morbidity, and mortality, and the wide array of successful treatment strategies, maintaining a high degree of suspicion for this condition, and understanding the potential treatment strategies is critical.

KEYWORDS

catheterization, extrinsic compression, left main, percutaneous coronary intervention, pulmonary hypertension

1 | INTRODUCTION

Pulmonary hypertension (PH) afflicts nearly 80 million patients worldwide and remains a severely debilitating condition with poor prognosis in the contemporary era despite marked therapeutic advancements in recent decades.[1,2] While the etiology of PH remains broad, the underlying pathophysiology shares a common final pathway of progressive pulmonary vasculopathy and remodeling leading to elevated pulmonary vascular resistance and subsequent right heart

Abbreviations: CABG, coronary artery bypass graft; CCTA, computed coronary tomography angiography; FFR, fractional flow reserve; IVUS, intravascular ultrasound; LMCA, left main coronary artery; MPI, myocardial perfusion imaging; MRI, magnetic resonance imaging; PA, pulmonary artery; PAH, pulmonary arterial hypertension; PAP, pulmonary arterial pressure; PCI, percutaneous coronary intervention; PH, pulmonary hypertension; SCD, sudden cardiac death; TTE, transthoracic echo.

Olcay Aksoy and Rushi V. Parikh contributed equally to this study.

failure.[2,3] The clinical manifestation of these processes is often non-specific symptoms including exertional dyspnea, fatigue, and angina.[3] Indeed, nearly 30% of patients with PH report angina, though the large majority of these patients have no significant angiographic evidence of coronary artery disease.[3,4] While the etiology of angina in PH remains controversial, increasing attention is being drawn to the possibility of left ventricular (LV) ischemia driving angina in this patient population. Specifically, multiple studies have reported the extrinsic compression of the left main coronary artery (LMCA) by a dilated pulmonary artery (PA).[4-7]

First described in 1957, LMCA compression is generally defined as ≥50% LMCA stenosis on coronary angiography due to a dilated main PA.[4,6,8] Indeed, a dilated PA can lead to significant eccentric narrowing and downward displacement of the LMCA causing ischemia.[8] Despite multiple case reports suggesting a low prevalence of LMCA compression in PH, larger studies have reported discordant findings with rates up to 40% in patients with angina or angina-like symptoms.[4] Ischemia due to LMCA compression has been associated with several complications including sudden cardiac death (SCD).[2] In fact, SCD has been reported in up to 26% of patients with severe primary arterial hypertension (PAH), the subtype of PH most commonly associated with LMCA compression.[9] Currently, the treatment for LMCA compression remains undefined with clinicians largely basing both pharmacologic and invasive therapies on anecdotal evidence and select case reports/series.[6,10,11] Given the high prevalence of LMCA compression in patients with PAH and the inherent morbidity and mortality, it is incumbent on physicians to better understand this phenomenon and potential therapeutic strategies. Hence, the aim of this systematic review is to provide a detailed account of the pathophysiology of LMCA compression in PAH as well as a framework for its diagnosis and management.

2 | PATHOPHYSIOLOGY

2.1 | Pulmonary arterial hypertension

The development of LMCA compression does not appear to be limited to the group or severity of PH, though most reported cases occur in the setting of PAH (i.e. Group 1 PH).[4,6,7,12,13] Interestingly, congenital heart disease appears to be the most common etiology of PAH underlying LMCA compression, and in particular, patients with atrial septal defects.[4,6,14,15] This finding is likely attributed to the relationship between PH duration and PA dilation, as further discussed below. Importantly; however, not all LMCA compression is caused by PAH or its sequelae, as rare cases of LMCA compression in the presence of a PA aneurysm without concomitant PAH have been reported.[12]

The true prevalence of LMCA compression in patients with PAH remains unknown. Despite early reports suggesting extrinsic compression of the LMCA to be an exceedingly rare event, more recent and larger studies have found higher rates (Table 1). One prospective study of 322 patients with PAH reported an approximately 6% prevalence of LMCA compression.[15] These findings were corroborated by another large prospective study of 765 patients with PAH, irrespective of symptoms.[4] In this larger study, only those with angina were actively screened for LMCA compression. Thus, the reported 6% prevalence likely represents an underestimation of the true proportion of patients with PAH suffering from LMCA compression.

2.2 | Pulmonary artery dilation

The persistently elevated pulmonary pressures in chronic PAH result from intimal thickening, medial hypertrophy, and luminal dilation in the proximal pulmonary vessels.[16] This vascular remodeling ultimately leads to significant PA dilation, which may in turn impinge upon nearby anatomic structures, namely the LMCA. While the etiology of PA dilation remains broad, the leading cause is PAH.[17,18] Interestingly, progression of dilation appears independent of PA pressures and cardiac output.[19] Instead, once dilated, further dilation appears to continue in an unremitting fashion despite aggressive optimal medical therapy (OMT), a finding that further encourages early screening and treatment of PH.[19] This may explain why LMCA compression is inconsistently correlated with PA pressures on echocardiography.[13]

Several studies have identified PA dilation as a risk factor in the development of LMCA compression (Table 1). This finding is consistent across a number of smaller case series, which found a PA diameter less than 40 mm to be sufficiently sensitive to rule out LMCA compression.[6,7] Furthermore, to effectively control for body surface area, sex, age, and cardiac phase, the ratio of the main PA: ascending aortic diameter ratio has been reported as a metric to assess PA dilation.[18,20] The three largest studies assessing LMCA compression via both TTE and CCTA found that an elevated main PA:aortic ratio ranging from ≥1.2 to 2.0 to be reasonably predictive of LMCA stenosis ≥50%.[4,6,7]

PA dilation causes LMCA compression by displacement of the LMCA downward and subsequent reduction of the takeoff angle.[4,7] As the downward displacement progresses, longer segments of the LMCA are compressed between the PA and left aortic sinus.[4] Notably, there have also been reports of patients with LMCA compression and PA diameters < 40 mm.[4] Thus, it is important to consider the individual anatomic variability with regards to structures that can extrinsically compress the LMCA.

2.3 | Structural anatomy

While a dilated PA is the principal risk factor for LMCA compression, not all patients with dilated PAs experience this phenomenon. The risk of LMCA compression is influenced by the origin of the vessel itself. Inferior displacement and/or rightward positioning of the left coronary ostium on the left coronary sinus may be more prone to compression from a dilated PA.[17,21] Conversely, a more leftward origin of the LMCA from the left coronary sinus may be protective against compression by a dilated PA.[7,11] Additionally, a reduced takeoff angle of the LMCA has been consistently observed in patients suffering

TABLE 1 Summary of literature[a] on left main coronary artery compression published in the last 20 years

Study	Etiology of pulmonary hypertension	Total number of patients	Prevalence of LMCA compression in patients with PAH	Prevalence of LMCA compression in patients with PAH + Angina	Screening test	Diagnostic test	Imaging findings		Predictors of LMCA compression	Intervention	Treatment success	Follow-up surveillance	Survival
							LMCA stenosis <50%	LMCA stenosis ≥ 50%					
Large Studies													
Galie et al. 2017	PAH (majority CHD)	765	6%	40%	CCTA	SCA (≥ 50% reduction of the LMCA luminal diameter)	CCTA: BS, mm 38 ± 8 PA/Ao diameters ratio 1.5 ± 0.3 LMCA take-off angle 49.6 ± 12.2°	CCTA: BS, mm 54 ± 17 PA/Ao diameters ratio 1.9 ± 0.6 LMCA take-off angle 34.1 ± 12.7°	CCTA: BS ≥ 40 mm - Sensitivity 83%, Specificity 70% PA/Ao diameters ratio ≥ 1.5 - Sensitivity 73%, Specificity 70% BS/BSA index ≥ 24 mm/m^2 - Sensitivity 79%, Specificity 68%	PCI (45) BMS (23) DES (22) PA Plasty (3)	PCI: 96% improvement in symptoms	9 months (SCA)	Cumulative survival 69% at 5-year follow-up[b]
Lee et al. 2017[c]	PAH (majority CHD)	322	6%	N/A	TTE	CCTA +/- SCA (≥ 50% reduction of the LMCA luminal diameter) [d]	TTE: PA diameter, mm 46.1 ± 4.8 CCTA: PA diameter, mm 42.4 ± 7.0 PA/Ao diameters ratio 1.6 ± 0.4	TTE: [e] PA diameter, mm 55.5 ± 11.6 CCTA: [e] PA diameter, mm 59.4 ± 13.0 PA/Ao diameters ratio 2.0 ± 0.7	TTE: [e] PA diameter ≥ 46.5 mm - Sensitivity 85.7%, Specificity 58.6% CCTA: PA diameter ≥ 45 mm - Sensitivity 90.5%, Specificity 69.2% PA/Ao diameters ratio AUC 0.836	N/A	N/A	N/A	N/A
Small Studies													
Vaseghi et al. 2010	PAH (majority idiopathic)	5	N/A	N/A	TTE/CCTA	SCA (≥ 50% reduction of the LMCA luminal diameter)	N/A	PA diameter, mm 63 ± 28	N/A	PCI (5) BMS (4) DES (1)	100% improvement in symptoms	3 months (CCTA)	N/A
Mesquita et al. 2003	PH (majority CHD)	36	19%	27%	TTE	SCA (≥ 50% reduction of the LMCA luminal diameter)	TTE: PA diameter, mm 37 ± 9 PA/Ao diameters ratio 1.46 ± 0.44	TTE: PA diameter, mm 55 ± 13 PA/Ao diameters ratio 1.98 ± 0.55	TTE: PA diameter, mm ≥ 40 mm - Sensitivity 100%, Specificity 58.6% PA/Ao diameters ratio ≥ 1.21 - Sensitivity 100%, Specificity 31.0%	PA Plasty (1) CABG (3)	100% improvement in symptoms	N/A	N/A
Kajita et al. 2001	PAH (majority CHD)	12	N/A	N/A	Aortogram and left. ventriculography	SCA (≥ 50% reduction of the LMCA luminal diameter)	SCA: PA/Ao diameters ratio N/A LMCA take-off angle 69.5 ± 15°	SCA: PA/Ao diameters ratio 2.1 ± 0.31 LMCA take-off angle 22.9 ± 13.4°	N/A	PA Plasty (1) CABG (2)	N/A	N/A	N/A

Abbreviations: Ao, aorta; AKI, acute kidney injury; BMS, bare metal stent; CABG, coronary artery bypass graft; CCTA, computed coronary tomography angiography; CHD, congenital heart disease; DES, drug-eluting stent; LMCA, left main coronary artery; N/A, not applicable; PA, pulmonary artery; PAH, pulmonary arterial hypertension; PCI, percutaneous coronary intervention; SCA, selective coronary angiography; TTE, transthoracic echocardiography.

[a]Excludes case reports and case series with sample sizes less than five.

[b]Based on a Research Correspondence published by Saia et al. 2019 in JACC: Cardiovascular Interventions.

[c]Includes both Lee et al. studies published in 2017 that examined overlapping sets of data.

[d]SCA was used inconsistently for confirmation of LMCA compression, which was defined as ≥ 50% reduction of the LMCA luminal diameter.

[e]Includes all mechanical complications identified by CCTA including extrinsic LMCA compression, PA dissection, PA thrombosis, and airway compression.

from LMCA compression.[4,7] Indeed, in patients with isolated coronary anomalies, a takeoff angle <45° has been found in the majority of patients who experienced SCD.[22] The takeoff angle of the LMCA is generated by two bisectors: the first is a central longitudinal line following the first part of the LMCA, and the second is parallel to the border of the left coronary sinus (Figure 1). In one study, patients with LMCA compression were noted to have a mean LMCA takeoff angle significantly more acute than that of the control population without LMCA disease or PA dilation.[7] This acute angle is thought to possibly result in kinking of the LMCA with subsequent stretching and/or compression of the vessel resulting in ischemia and SCD.[23]

2.4 | Angina

The most common clinical presentation of LMCA compression is angina.[4,10] Nearly 30% of patients with PAH experience chest discomfort, though the mechanism remains unclear.[3,24] Originally, pulmonary artery distension with subsequent activation of pain receptors was proposed to account for chest discomfort in patients with PAH.[25] However, this theory gave way to the idea that angina could be attributed to progressive RV dilation from pressure overload with subsequent hypertrophy and subendocardial ischemia.[2,3,5,25,26] The absence of atherosclerotic disease in the vast majority of patients who presented with this condition further supports this hypothesis.

More recently, a number of studies have been published identifying LMCA compression due to PA dilation with resultant LV ischemia as an underdiagnosed cause of angina in PAH.[4,10,27] Angina has been found to be associated with younger patients, higher pulmonary arterial pressures (PAP), and larger PA diameters compared to patients without angina.[6] In the largest case series of 121 patients with PAH and angina, 48 (40%) had confirmed LMCA stenosis ≥50%.[4]

Given the significant disease burden of PAH and high prevalence of angina associated with LMCA compression, this phenomenon should be considered for any patient with PAH complaining of angina. However, not all patients with LMCA compression in the setting of PAH complain of angina (Table 1). Thus, while angina in patients with PAH should prompt further investigation, its absence should not preclude appropriate workup in the setting of PA dilation. Indeed, some patients complain only of dyspnea and/or fatigue, non-specific complaints that may delay diagnosis and subsequent management.[3,24]

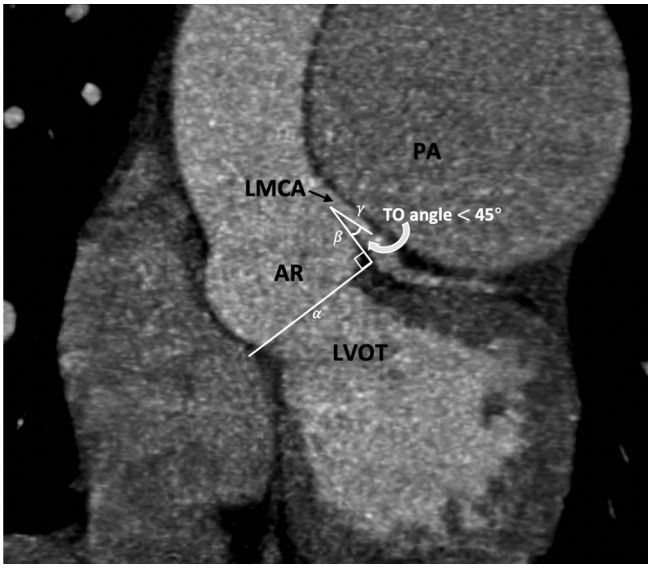

FIGURE 1 Assessment of the LMCA take-off angle in the oblique coronal view of multiplanar CCTA. The take-off (TO) angle is generated by 2 bisectors: 1 is represented by the central longitudinal line of the first part of the LMCA (γ), and the second bisector (β) is orthogonal (90°) to the aortic valve annulus plane (α). AR, aortic root; LMCA, left main coronary artery; LVOT, left ventricular outflow tract; PA, pulmonary artery

2.5 | Left ventricular dysfunction

Up to 20% of patients with severe PAH have LV dysfunction, the mechanism of which remains poorly understood.[28] One hypothesis is pulmonary vascular resistance increasing over time resulting in right heart strain with subsequent remodeling and RV dilation, leading to interventricular septal flattening and asynchrony, and ultimately progression to biventricular dysfunction. Indeed, much emphasis has been placed on the role of ventricular interdependence with regards to progressive RV failure causing a reduction in LV compliance.[28,29] However, as reports of LMCA compression continue to surface, so too does evidence of LV ischemia leading to LV dysfunction in this patient population. In fact, multiple case studies have demonstrated reversible LV ischemia and associated dysfunction following treatment of LMCA compression with both medical and invasive therapies.[5,10] Thus, while further studies are needed to determine the underlying etiology of LV dysfunction in this patient population, patients presenting with PAH and signs or symptoms of left-sided heart failure should prompt consideration of LMCA compression.

2.6 | Sudden cardiac death

Compression of the LMCA may present as SCD, which has been reported as a major cause of death in the PAH population.[2] In fact, a large retrospective report identified that PA dilation is an independent risk factor for SCD in patients with PAH.[30] Indeed, given that the first presentation of LMCA compression is often SCD, its prevalence is likely underestimated in the literature.[2,15] Ventricular tachyarrhythmias as a result of LV ischemia are thought to be the cause of SCD in patients suffering from LMCA compression.[29,31] Further support for the anatomical basis of LMCA compression and the risk of SCD come from multiple studies on anomalous coronary arteries and their attendant risks.[21-23] Specifically, both acute angle takeoff of a LMCA and coursing of an anomalous coronary artery between the aorta and pulmonary artery have been associated with a risk of SCD.[22,23] Thus, earlier diagnosis and treatment of LMCA compression may lower the mortality rate in this patient population.

3 | DIAGNOSIS

Given the varying presentation of LMCA compression, a high degree of clinical suspicion is required to make the diagnosis. Indeed, LMCA compression notwithstanding, PAH remains an insidious disease process that takes on average 1.1 years from symptom presentation to diagnosis.[32] Furthermore, given the progressive and unremitting nature of PAH, late diagnosis has been associated with poor prognosis and increased mortality.[3] Consequently, in the absence of any pathognomonic symptomatology, the early diagnosis of LMCA compression relies primarily on imaging.

3.1 | Echocardiography

Transthoracic echocardiography (TTE) is widely used as the initial screening tool in the assessment of suspected PH.[33] Yet, the use of TTE to measure PA dilation in daily clinical practice remains underutilized. In one series of 298 patients with PAH, 15% (*n*=46) had a main PA diameter >40mm, of which 33% (*n*=15) were identified with LMCA compression. Notably, a main PA diameter ≥46.5 mm on TTE reliably predicted the presence of mechanical complications, including LMCA compression (Table 1).[13] Given these findings, and in accordance with the European Society of Cardiology and the European Respiratory Society guidelines, measuring PA diameter by TTE during routine and recommended follow-up of patients with PAH should be implemented.[33] Such assessments, using existing screening and surveillance imaging protocols, would inform and guide further investigation of LMCA compression using higher resolution imaging modalities. Further studies are needed to clarify the PA diameter at which clinicians should consider further work-up. Currently, the use of TTE as a screening tool in patients with PAH varies considerably among providers. In our institutional experience, a PA diameter of 40mm in the appropriate clinical context often prompts additional diagnostic imaging.

3.2 | Computed coronary tomography angiography (CCTA)

Given the ability of CCTA to accurately and reliably measure PA dilation and acute takeoff angle of the LMCA, it has emerged as the dominant imaging modality to evaluate LMCA compression in patients with PAH.[14,34] The first large prospective study to assess the safety and utility of CCTA screening for LMCA compression in patients with PAH and angina reported a strong concordance between findings concerning for LMCA compression on CCTA and confirmed stenosis on coronary angiography.[4] Specifically, this study identified CCTA findings of a LMCA takeoff angle <60° and/or significant LMCA stenosis ≥50% as predictors of true LMCA compression (Figure 2). Furthermore, both PA diameter and an elevated PA/aortic ratio were correlated with angiographically-verified LMCA stenosis (Table 1). Accordingly, CCTA should be favored in the diagnostic workup in patients with low-intermediate probability of significant extrinsic compression. Conversely, in patients with high-risk features of LMCA compression, coronary angiography should be considered.[4]

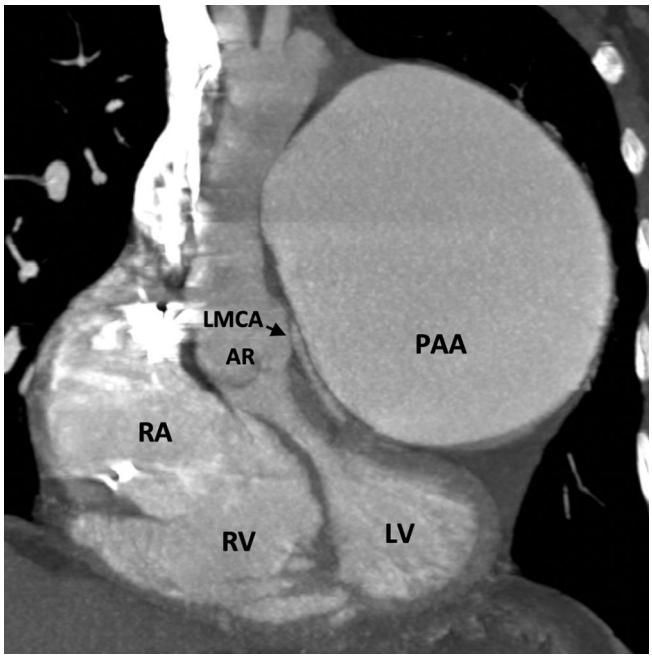

FIGURE 2 Coronal CCTA in a 58-year-old female with severe PAH and significant LMCA compression by a massive PAA measuring 11 cm. The LMCA is acutely angled at the take-off of the coronary sinus. AR, aortic root; CCTA, computed coronary tomography angiography; LMCA, left main coronary artery; LV, left ventricle; PAA, pulmonary artery aneurysm; PAH, pulmonary arterial hypertension; RA, right atrium; RV, right ventricle

3.3 | Magnetic resonance imaging

Magnetic resonance imaging (MRI) can also provide useful information about cardiac structure and function in the setting of LMCA compression.[17] Importantly, there is no study directly comparing CCTA with MRI for LMCA compression. However, given constraints, such as, incompatible medical equipment (e.g. older generation pacemakers) and the superior temporal resolution of CCTA, MRI is less commonly used in the evaluation of LCMA compression.

3.4 | Coronary angiography

While certain non-invasive imaging modalities have proven effective as screening tools, invasive coronary angiography remains the gold standard for the diagnosis of LMCA compression.[4-7] LMCA compression is typically best visualized in the left anterior oblique cranial view.[4,7] This view allows the origin of the LMCA to be distinguished from the aortic profile without obstruction from the left aortic sinus. Characteristic findings of LMCA compression include the presence of

an eccentric slit-like lumen, which is often associated with the downward displacement of the LMCA.[4,7] Unlike typical atherosclerotic lesions, extrinsic compression of the LMCA often appears as an eccentric narrowing at the ostium with a subsequent smooth post-obstructive reconstitution of the vessel (Figure 3).[6,35] Additionally, simultaneous coronary and pulmonary angiography can help determine if a dilated PA is the cause of LMCA compression.[36]

Intracoronary imaging, such as, intravascular ultrasound (IVUS) can also serve as a valuable tool to help delineate the etiology of LMCA stenosis.[10,14,34,37] In LMCA compression, IVUS consistently demonstrates an asymmetric, oval-shaped lumen with a slit-like narrowing of the ostium (Figure 3).[12,34] Additionally, compared with coronary angiography, IVUS allows for superior assessment of both the diameter and length of the lesion and can identify atherosclerotic plaque.[38]

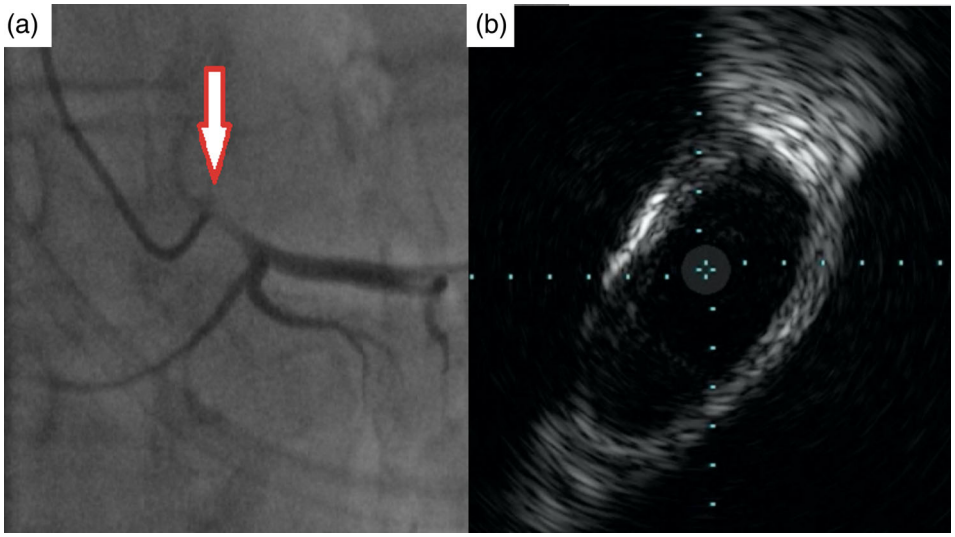

FIGURE 3 Coronary angiography (a) demonstrates LMCA compression (red arrow) in the setting of a dilated PA with ostial narrowing and smooth post-obstructive reconstitution of the vessel. Cross-sectional intravascular ultrasound view (b) of LMCA compression with evidence of an asymmetric oval-shaped lumen and no sign of atherosclerosis. LMCA, left main coronary artery; PA, pulmonary artery [Color figure can be viewed at wileyonlinelibrary.com]

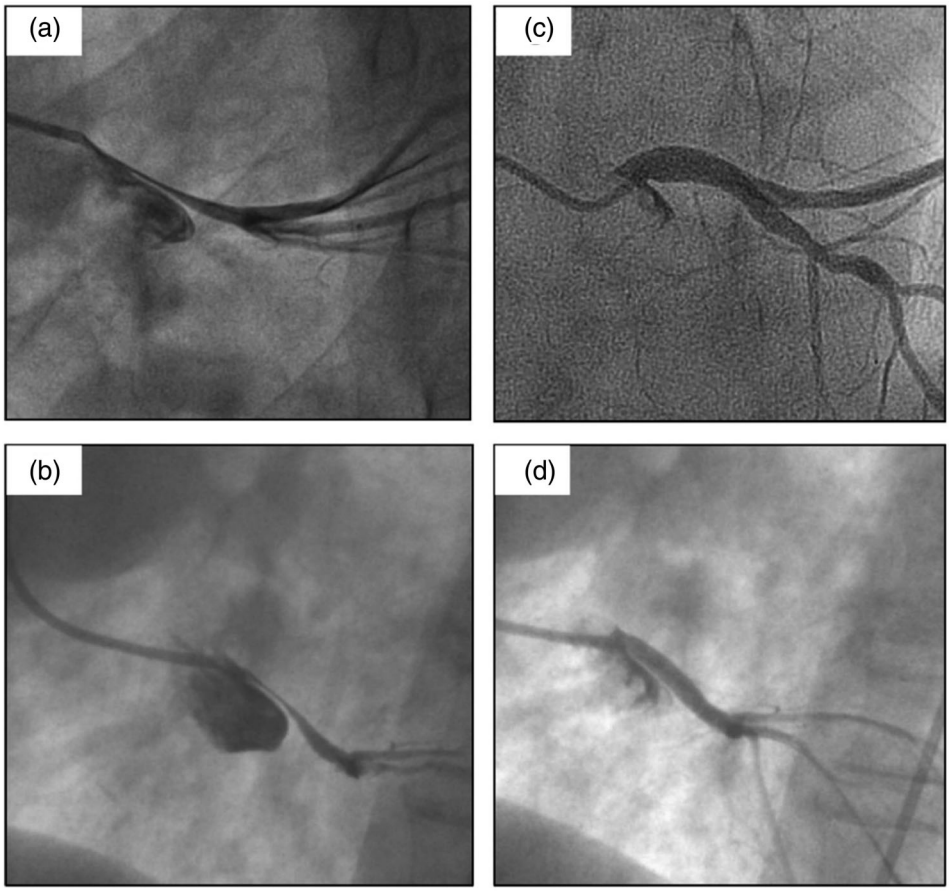

FIGURE 4 In compressed LMCAs due to dilated main PAs, (a) and (b) severe segmental stenoses starting at the ostium can be seen; (c) and (d) here are recanalized LMCAs after percutaneous coronary intervention with stenting. LMCA, left main coronary artery; PA, pulmonary artery.
Source: Reprinted from J Am Coll Cardiol., 69/23, Galie et al., Left Main Coronary Artery Compression in PAH, 2808-17, (2017) with permission from Elsevier

Fractional flow reserve (FFR) has also been frequently used to assess the hemodynamic significance of extrinsic compression on the LMCA by a dilated PA.[37] However, due to the dynamic nature of extrinsic LMCA compression, FFR may underestimate the hemodynamic significance of LMCA compression.[10] Thus, an invasive approach using angiography along with concomitant intracoronary imaging +/- physiology may provide the comprehensive data required to guide management of LMCA compression.

Finally, it should be noted that the introduction of a guiding and/or IVUS catheter into the LMCA may restore the reduced take-off angle caused by a dilated PA and thereby relieve the obstruction, which may be misleading. Instead, nonselective contrast injection of the left aortic sinus may allow for the assessment of the LMCA while avoiding the potential interference of equipment within the artery itself.[4]

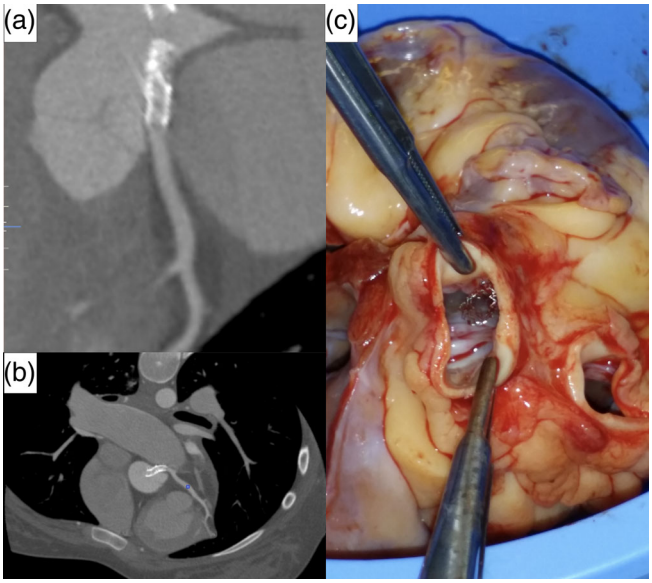

FIGURE 5 Stent failure due to recoil (a) and migration (b) in a 22-year-old female patient with severe PAH treated for LMCA compression. The patient ultimately underwent combined heart-lung transplantation; the explanted heart (c) demonstrates the left main stent extending into the aorta. LMCA, left main coronary artery; PAH, pulmonary arterial hypertension [Color figure can be viewed at wileyonlinelibrary.com]

4 | MANAGEMENT

4.1 | Medical management

Given that LMCA compression may be caused by PA dilation in the setting of progressive PAH, pharmacologic treatment of PAH may reduce compression-related symptoms.[19] Multiple case reports have highlighted both the resolution of angina and improvement in biventricular function in patients presenting with LMCA compression treated with advanced therapies for PAH (e.g. endothelin receptor antagonists, prostacyclins, and phosphodiesterase-5 inhibitors).[10,37]

4.2 | Invasive management

While the treatment of LMCA compression remains controversial, PCI has emerged as an increasingly attractive management strategy. First described in 2001, stenting the LMCA in a patient with PAH and LMCA compression may lead to resolution of angina and significant improvement in LV dysfunction.[5] This and subsequent studies evaluating the role of PCI in this scenario have challenged the widely accepted belief that significant LMCA stenosis requires surgical intervention.[39] PCI avoids the risk of cardiopulmonary bypass, and the typical ostial location of the stenosis and the lack of significant atherosclerosis makes it a relatively low-risk procedure, a finding that has been borne out in both short- and intermediate-term follow-up.[4,5,33,40,41] Indeed, PCI is not only technically feasible (Figure 4), but it is often performed with a single stent and is associated with low rates of residual angina and restenosis (Table 1).[4,35,40] In fact, in one recent prospective study, the majority of patients who underwent PCI in the setting of LMCA compression achieved sustained resolution of

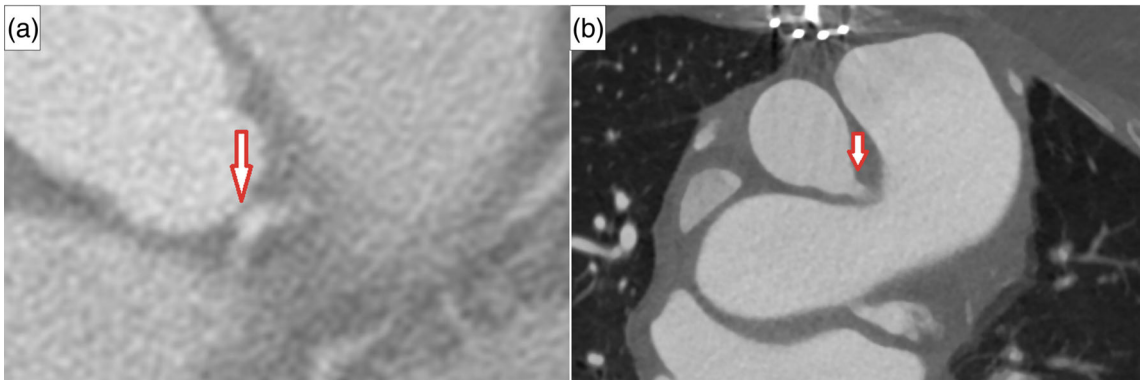

FIGURE 6 LMCA compression in the setting of a dilated PA pre- and post-lung transplantation. (a) CCTA image with evidence of severe LMCA stenosis (red arrow). (b) CCTA of post-lung transplant with subsequent resolution (red arrow) of LMCA compression. CCTA, computed coronary tomography angiography; LMCA, left main coronary artery; PA, pulmonary artery [Color figure can be viewed at wileyonlinelibrary.com]

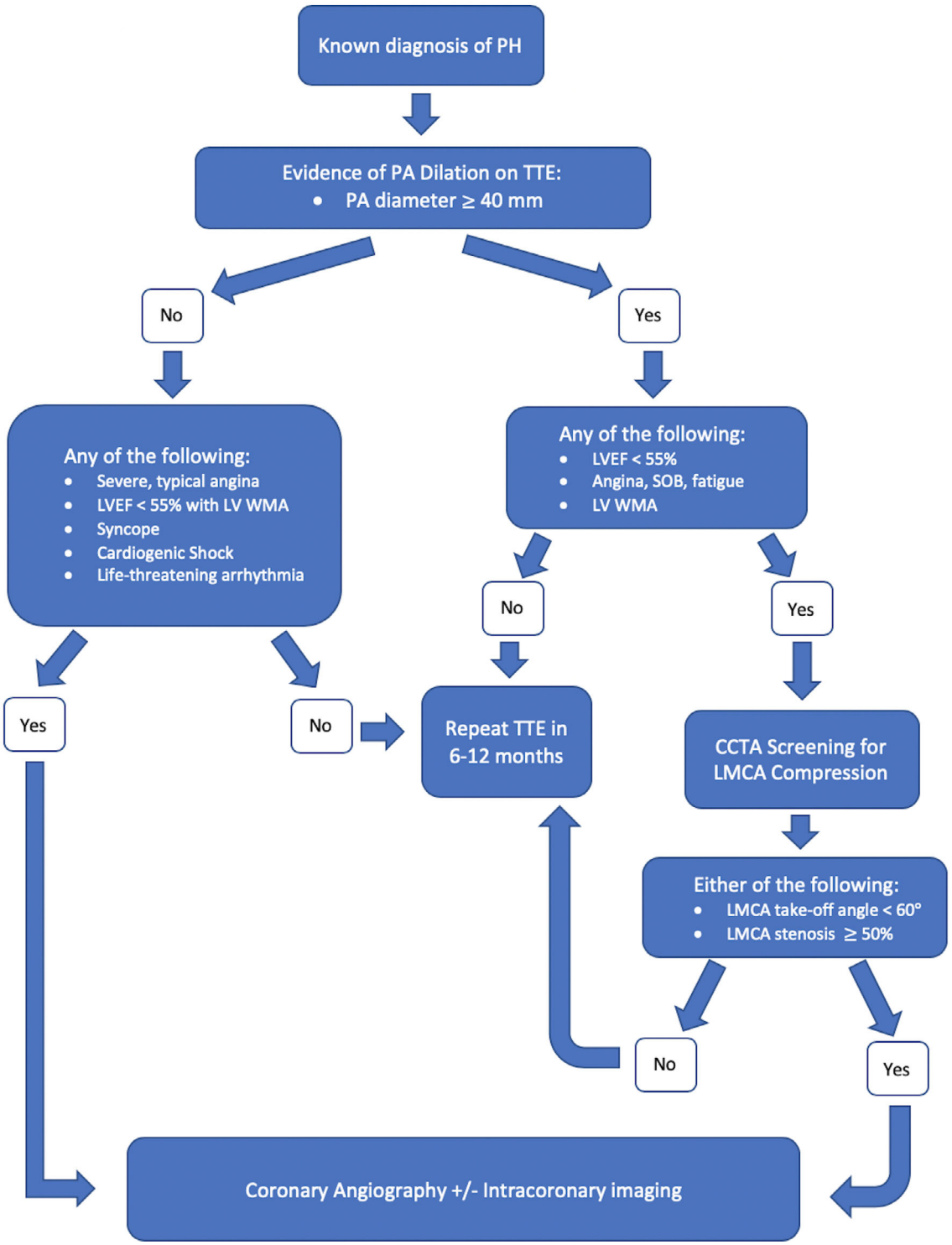

FIGURE 7 Screening algorithm for LMCA compression in patients with PH. CA, coronary angiography; CCTA, coronary computed tomography angiography; LMCA, left main coronary artery; LV, left ventricle; LVEF, left ventricular ejection fraction; PH, pulmonary hypertension; SOB, shortness of breath; TTE, transthoracic echo; WMA, wall motion abnormalities [Color figure can be viewed at wileyonlinelibrary.com]

angina.[4] All patients tolerated PCI and both short- and long-term follow-up, up to 5 years, has demonstrated promising and safe results.[4,40] Notwithstanding the durable benefit with respect to angina relief, larger, longer-term studies are needed to determine if PCI reduces mortality among patients with LMCA compression.

While stent choice has varied in prior studies, drug-eluting stents are largely favored in contemporary practice. The decision is often mediated by several factors including LMCA diameter, bleeding profile, and likelihood of imminent surgery, such as, heart-lung transplantation.[11,27] Restenosis and/or stent failure appear predominantly

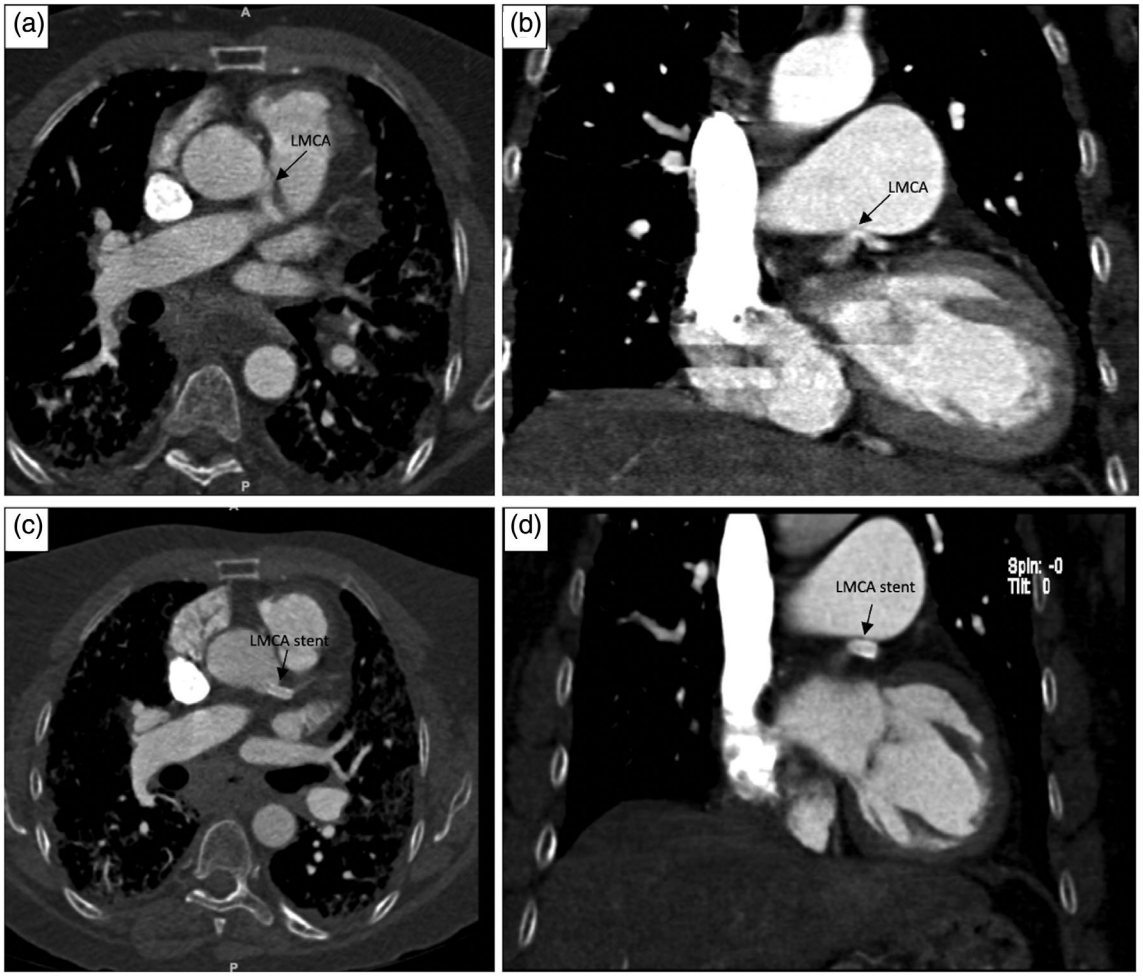

FIGURE 8 57-year-old female with severe PAH and a dilated PA causing significant LMCA compression (a) and kinking (b). CCTA axial (c) and coronal (d) views demonstrate a widely patent stent post-PCI. CCTA, computed coronary tomography angiography; LMCA, left main coronary artery; PA, pulmonary artery; PAH, pulmonary arterial hypertension; PCI, percutaneous coronary intervention

mediated by mechanical recoil, neointimal hyperplasia, and geographical miss.[4] Mechanical recoil in this context appears to occur from structural collapse due to extrinsic compression from a dilated PA (Figure 5).[42] Neointimal hyperplasia is a rare but observed event. And incomplete ostial coverage with residual stenosis has been reported as well.[40]

4.3 | Surgery

Although coronary artery bypass surgery (CABG) remains the gold-standard for patients with atherosclerotic LMCA disease, extrinsic compression of the LMCA due to a dilated PA in the setting of PAH represents a different phenomenon. The presence of PAH increases the risk of both morbidity and mortality during cardiac surgery, thereby making PCI the more attractive strategy in many instances.[33,35] However, if a patient otherwise requires cardiac surgery for another condition (e.g. valvular heart disease), CABG should be pursued. Notably, there have been no direct comparisons between surgery and PCI in the treatment of LMCA compression. Several iterations of surgical interventions have been reported as successful, including CABG, PA-plasty, correction of underlying congenital heart disease, and lung or heart-lung transplantation (Figure 6).[4,6,21,34,35]

5 | SCREENING AND SURVEILLANCE

5.1 | Screening

There remains a paucity of evidence available regarding appropriate screening algorithms and protocols for LMCA compression in the setting of PAH. While one study recently reported the successful use of CCTA in identifying patients with PAH and significant LMCA compression, it was limited to symptomatic patients.[4] As previously described, this debilitating and lethal disease process has been identified in asymptomatic patients.[15] Therefore, effective screening algorithms for all patients independent of symptoms are needed. Based on the data reviewed herein, we propose the following multimodal screening algorithm for PA dilation and subsequently LMCA compression in patients with PAH (Figure 7). Importantly, given inter-operator

variability in assessing PA diameter on TTE, an indeterminate study in the setting of concerning symptoms should trigger additional imaging.

5.2 | Surveillance

Best practices for short- and long-term surveillance following both medical and interventional therapy for LMCA compression remain undefined. Patients with LMCA compression in the setting of PAH who are treated with OMT should be surveilled by routine TTE every 6–12 months with particular attention paid to changes in PA diameter and LV function.[33] Should the patient develop worsening symptoms, urgent coronary angiography should strongly be considered given the high suspicion for worsening LMCA compression (Figure 7).

Post-LMCA PCI imaging surveillance remains controversial with providers using varying imaging modalities, including CCTA (Figure 8) and invasive coronary angiography, to assess for stent position and patency (Table 1).[4,11] Notably, once stented, despite unremitting dilation of the PA, patients appear relatively protected from further LMCA extrinsic compression.[11] Taken together, we do not endorse routine post-PCI imaging, but rather recommend that surveillance be guided by symptoms and clinical context.

6 | CONCLUSION

Over six decades after its initial pathological description in 1957, extrinsic compression of the LMCA by a dilated PA in the setting of PAH is an increasingly recognized and treated entity. Given the prevalence of LMCA compression, its associated risks, and the wide array of effective treatment options, maintaining a high degree of suspicion for this condition and intervening in a timely fashion remains critical. Thus, a multidisciplinary team effort involving specialists from the fields of pulmonary hypertension, cardiac imaging, interventional cardiology, cardiothoracic surgery, and heart/lung transplantation is required to provide individualized and nuanced care for patients with this challenging disease phenomenon.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Jonathan E. Labin https://orcid.org/0000-0002-6483-697X
Gentian Lluri https://orcid.org/0000-0002-4000-8993

REFERENCES

1. Hoeper MM, Humbert M, Souza R, et al. A global view of pulmonary hypertension. Lancet Respir Med. 2016;4(4):306-322.
2. Demerouti EA, Manginas AN, Athanassopoulos GD, Karatasakis GT. Complications leading to sudden cardiac death in pulmonary arterial hypertension. Respir Care. 2013;58(7):1246-1254.
3. Rich S, Dantzker DR, Ayres SM, et al. Primary pulmonary hypertension: a national prospective study. Ann Intern Med. 1987;107(2):216-223.
4. Galiè N, Saia F, Palazzini M, et al. Left main coronary artery compression in patients with pulmonary arterial hypertension and angina. J Am Coll Cardiol. 2017;69(23):2808-2817.
5. Rich S, McLaughlin VV, O'neill W. Stenting to reverse left ventricular ischemia due to left main coronary artery compression in primary pulmonary hypertension. Chest. 2001;120(4):1412-1415.
6. Mesquita SMF, Castro CRP, Ikari NM, Oliveira SA, Lopes AA. Likelihood of left main coronary artery compression based on pulmonary trunk diameter in patients with pulmonary hypertension. Am J Med. 2004;116(6):369-374.
7. Kajita LJ, Martinez EE, Ambrose JA, et al. Extrinsic compression of the left main coronary artery by a dilated pulmonary artery: clinical, angiographic, and hemodynamic determinants. Catheter Cardiovasc Interv. 2001;52(1):49-54.
8. Corday E, Gold H, Kaplan L. Coronary artery compression; an explanation for the cause of coronary insufficiency in pulmonary hypertension. Trans Am Coll Cardiol. 1957;7:93-103.
9. D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension: results from a national prospective registry. Ann Intern Med. 1991;115(5):343-349.
10. de Jesus Perez VA, Haddad F, Vagelos RH, et al. Angina associated with left main coronary artery compression in pulmonary hypertension. J Heart Lung Transplant. 2009;28(5):527-530.
11. Vaseghi M, Lee MS, Currier J, Tobis J, Shapiro S, Aboulhosn J. Percutaneous intervention of left main coronary artery compression by pulmonary artery aneurysm. Catheter Cardiovasc Interv. 2010;76(3):352-356.
12. Defaria Yeh D, Ghoshhajra B, Inglessis-Azuaje I, MacGillivray T, Liberthson R, Bhatt AB. Massive pulmonary artery aneurysm: causing left main coronary artery compression in the absence of pulmonary hypertension. Texas Hear Inst J. 2015;42(5):465-467.
13. Lee SE, An HY, Im JH, et al. Screening of mechanical complications of dilated pulmonary artery related to the risk for sudden cardiac death in patients with pulmonary arterial hypertension by transthoracic echocardiography. J Am Soc Echocardiogr. 2016;29(6):561-566.
14. Dodd JD, Maree A, Palacios I, et al. Left main coronary artery compression syndrome: evaluation with 64-slice cardiac multidetector computed tomography. Circulation. 2007;115(1):10-11.
15. Lee SE, Im JH, Sung JM, et al. Detection of mechanical complications related to the potential risk of sudden cardiac death in patients with pulmonary arterial hypertension by computed tomography. Int J Cardiol. 2017;243:460-465.
16. Stacher E, Graham BB, Hunt JM, et al. Modern age pathology of pulmonary arterial hypertension. Am J Respir Crit Care Med. 2012;186(3):261-272.
17. Dakkak W, Tonelli AR. Compression of adjacent anatomical structures by pulmonary artery dilation. Postgrad Med. 2016;128(5):451-459.
18. Raymond TE, Khabbaza JE, Yadav R, Tonelli AR. Significance of main pulmonary artery dilation on imaging studies. Ann Am Thorac Soc. 2014;11(10):1623-1632.
19. Boerrigter B, Mauritz GJ, Marcus JT, et al. Progressive dilatation of the main pulmonary artery is a characteristic of pulmonary arterial hypertension and is not related to changes in pressure. Chest. 2010;138(6):1395-1401.
20. Murray TI, Boxt LM, Katz J, Reagan K, Barst RJ. Estimation of pulmonary artery pressure in patients with primary pulmonary hypertension by quantitative analysis of magnetic resonance images. J Thorac Imaging. 1994;9(3):198-204.

21. Fujiwara K, Naito Y, Higashiue SI, et al. Left main coronary trunk compression by dilated main pulmonary artery in atrial septal defect: report of three cases. J Thorac Cardiovasc Surg. 1992;104(2):449-452.
22. Taylor AJ, Rogan KM, Virmani R. Sudden cardiac death associated with isolated congenital coronary artery anomalies. J Am Coll Cardiol. 1992;20(3):640-647.
23. Finocchiaro G, Behr ER, Tanzarella G, et al. Anomalous coronary artery origin and sudden cardiac death: clinical and pathological insights from a national pathology registry. J Am Coll Cardiol Clin Electrophysiol. 2019;5(4):516-522.
24. Brown LM, Chen H, Halpern S, et al. Delay in recognition of pulmonary arterial hypertension: factors identified from the REVEAL registry. Chest. 2011;140(1):19-26.
25. Viar WN, Harrison TR. Chest pain in association with pulmonary hypertension: its similarity to the pain of coronary disease. Circulation. 1952;5:1-11.
26. Gómez A, Bialostozky D, Zajarias A, et al. Right ventricular ischemia in patients with primary pulmonary hypertension. J Am Coll Cardiol. 2001;38(4):1137-1142.
27. Ikegami R, Ozaki K, Ozawa T, Hirono S, Ito M, Minamino T. Percutaneous coronary intervention for a patient with left main coronary compression syndrome. Intern Med. 2018;57(10):1421-1424.
28. Vizza CD, Lynch JP, Ochoa LL, Richardson G, Trulock EP. Right and left ventricular dysfunction in patients with severe pulmonary disease. Chest. 1998;113(3):576-583.
29. Delcroix M, Naeije R. Optimising the management of pulmonary arterial hypertension patients: emergency treatments. Eur Respir Rev. 2010;19(117):204-211.
30. Żyłkowska J, Kurzyna M, Florczyk M, et al. Pulmonary artery dilatation correlates with the risk of unexpected death in chronic arterial or thromboembolic pulmonary hypertension. Chest. 2012;142(6):1406-1416.
31. Sahay S, Tonelli AR. Ventricular fibrillation caused by extrinsic compression of the left main coronary artery. Heart. 2013;99(12):895-896.
32. Badesch DB, Raskob GE, Elliott CG, et al. Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. Chest. 2010;137(2):376-387.
33. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2016;37(1):67-119.
34. Bonderman D, Fleischmann D, Prokop M, Klepetko W, Lang IM. Left main coronary artery compression by the pulmonary trunk in pulmonary hypertension. Circulation. 2002;105(2):265.
35. Lee MS, Oyama J, Bhatia R, Kim YH, Park SJ. Left main coronary artery compression from pulmonary artery enlargement due to pulmonary hypertension: a contemporary review and argument for percutaneous revascularization. Catheter Cardiovasc Interv. 2010;76(4):543-550.
36. Ihdayhid AR, Asrar ul Haq M, Dembo L, Yong G. Simultaneous coronary and pulmonary angiography to diagnose critical left main coronary artery stenosis secondary to dilated pulmonary artery. J Am Coll Cardiol Cardiovasc Interv. 2016;9(11):1193-1194.
37. Beg F, Barker CM, Zoghbi WA. Left main coronary trunk compression by a severely enlarged pulmonary artery: noninvasive and invasive assessment. J Am Coll Cardiol Cardiovasc Interv. 2019;12(3):314-316.
38. Park SJ, Kim YH, Park DW, et al. Impact of intravascular ultrasound guidance on long-term mortality in stenting for unprotected left main coronary artery stenosis. Circ: Cardiovasc Interv. 2009;2(3):167-177.
39. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. New Engl J Med. 2009;360(10):961-972.
40. Saia F, Dall'Ara G, Marzocchi A, et al. Left main coronary artery extrinsic compression in patients with pulmonary arterial hypertension: technical insights and long-term clinical outcomes after stenting. J Am Coll Cardiol Cardiovasc Interv. 2019;12(3):319-321.
41. Chieffo A, Park SJ, Valgimigli M, et al. Favorable long-term outcome after drug-eluting stent implantation in nonbifurcation lesions that involve unprotected left main coronary artery: a multicenter registry. Circulation. 2007;116(2):158-162.
42. Adigopula S, Nsair A. Left main coronary artery stent migration. New Engl J Med. 2015;373(20):1957-1957.

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