

Definition and Management of Segmental Pulmonary Hypertension

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The World Pulmonary Hypertension Symposium in 2013 (Nice, France) introduced a new entity in the classification for pediatric and adult patients called “segmental pulmonary hypertension (PH).”¹ Segmental PH was described in the international 2015 guidelines as PH “observed in discrete lung areas perfused by aortopulmonary collaterals in congenital heart diseases such as pulmonary or tricuspid atresia,”² while the proceedings of the Nice World Symposium¹ defined this as “PH in one or more lobes of one or both lungs.” Others have defined segmental PH more broadly as PH that does not follow a homogeneous distribution, with some parts of the pulmonary vasculature being exposed to higher pressures than others.³

This entity was included under the umbrella of World Heart Organization group 5 (PH caused by unclear or multifactorial mechanisms), because little is known about its pathophysiology and response to pulmonary arterial hypertension (PAH) therapies.^{1,2} Segmental PH is most commonly encountered in patients with congenital heart disease (CHD) and carries notable similarities to PAH (Group 1.4.4, PAH associated with CHD) and group 4 of the PH classification (Group 4.2.4 PH in patients with congenital pulmonary artery [PA] stenoses), yet there is no systematic description of the broad spectrum of conditions encompassed by this entity or its distinct pathophysiological features and how these may affect management.

We present herewith a consensus statement on segmental PH, including a working definition, range of conditions that may be classified under this entity, description of pathophysiology in terms of pulmonary vasculature, cardiovascular anatomy, and management principles.

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J Am Heart Assoc. 2018;7:e008587. DOI: 10.1161/JAHA.118.008587.

Received January 8, 2018; accepted March 29, 2018.

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Definition and Classification of Segmental PH

The term “segmental” indicates that segments of the lung rather than the entire lung are affected by pulmonary vascular remodeling and PH (ie, parts of 1 or more lobes, a single lung, etc.). As such, at least 1 segment of the pulmonary vasculature is nonhypertensive. While macroscopic branch pulmonary artery stenosis may be associated with the development of segmental PH, the term “segmental PH” does not refer to disease of the segmental pulmonary arteries (ie, stenosis of medium-sized pulmonary arteries that run alongside segmental bronchi) per se, though segmental PH is often observed in that setting (eg, Alagille syndrome). A unified definition of segmental PH should include the following concepts:

1. A condition of 1 or more but not all segments of the lung.
2. Each hypertensive area of the lung may present with PH of different severity.
3. Symptoms of segmental PH often depend on the severity of ventilation-to-perfusion (V/Q) mismatch and right (subpulmonary) heart failure.

- a. In patients with segmental PH, significant differences in lung perfusion in various lung segments are likely to adversely affect V/Q ratio and blood oxygenation. This is distinct from inhomogeneity in the V/Q observed in normal people (eg, greater towards the apex).
 - b. Lung segments supplied by collaterals arising from the aorta receive partially (or fully) oxygenated blood, hence, again causing an increase in physiological dead space.
 - c. Co-existing right-to-left shunting is common and contributes further to V/Q mismatch.
4. Affected lung segments may or may not be in direct communication with the right (or subpulmonary) ventricle.
 5. Segments of the pulmonary vasculature that are in direct (unobstructed) communication will have identical pulmonary pressures, even if peripheral resistances differ. This is also true in the case of pulmonary vein stenoses, which can raise pulmonary wedge pressure in 1 or often more lung segments, but will not cause a segmental rise in pulmonary arterial pressure or a rise in PVR.
 6. Separate detailed assessment of PA pressures and calculation of pulmonary vascular resistance (PVR) in each lung segment is required to fully understand lung pathophysiology and the severity of PH in these patients. This often, however, proves difficult even in expert hands.

In this article, we propose the following definition of segmental PH: Segmental pulmonary hypertension encompasses any condition with abnormal underlying cardiac or vascular anatomy, usually including varied sources of pulmonary blood supply, which results in distal pulmonary vascular disease that affects various lung segments to differing degrees.

Lung perfusion and the relation between the heart and the pulmonary vascular tree varies significantly within the spectrum of segmental pulmonary hypertension and may affect presentation and the response to therapies. Hence, we propose the following classification for segmental PH:

1. Right ventricle (RV) communicating directly with the entire pulmonary vascular bed (eg, large ventricular septal defect [VSD] with peripheral pulmonary stenosis (PS) and ventriculo-arterial concordance).
2. RV supplies part of the pulmonary vascular bed (eg, congenital absence/interruption of a pulmonary artery supplied by large collaterals/isolated pulmonary artery of ductal origin or a patent ductus arteriosus [PDA], hemitruncus arteriosus).
3. RV with no direct communication with the pulmonary vascular bed:

- a. With well-formed (native) PAs (eg, truncus arteriosus with PA stenosis);
- b. With ill-formed PAs and a pulmonary circulation supplied by collateral arteries, a PDA, or surgical shunts (eg, tetralogy of Fallot [TOF] with pulmonary atresia, often referred to as complex pulmonary atresia throughout this article).

There are cases in which the subpulmonary ventricle is a morphologic left ventricle; the current article uses the term RV to refer to the subpulmonary ventricle, independent of anatomic characteristics.

Conditions in Which Segmental PH May Develop

Congenital lesions that may lead to segmental PH include complex pulmonary atresia, hemitruncus arteriosus, absence/atresia of a single pulmonary artery, and an anomalous pulmonary artery from the aorta feeding a single lung segment (Figure 1). Moreover, any large post-tricuspid cardiac defect (eg, VSD atrioventricular septal defect, PDA, aortopulmonary window, or truncus arteriosus) that may lead to increased PVR (ie, Eisenmenger physiology) can result in segmental PH when peripheral PA stenosis is present, whether naturally or because of failed PA banding. In these cases, the PA stenosis effectively “protects” some but not all segments of the lung from developing pulmonary vascular disease. Finally, surgical shunts (eg, Potts or Waterston shunt) that may supply only part of the pulmonary vascular bed (eg, disconnected PAs), or cause localized branch PA stenosis, can lead to segmental PH. Specific examples of these congenital variants are considered below. Of note, in conditions such as Alagille syndrome, branch PA stenosis may result in PH in unobstructed segments of the lung in the absence of an intracardiac defect, somewhat resembling chronic thromboembolic PH in pathophysiology. Such conditions are mentioned in the international PH classification under group 4 (chronic thromboembolic PH and other PA obstructions, group 4.2.4).²

Pulmonary Atresia

Pulmonary atresia is encountered in association with numerous congenital heart defects, and there is no universal agreement on its anatomic and clinical classification.^{4,5} Two main forms exist. The first, pulmonary atresia with a VSD and a biventricular circulation, is generally considered part of the spectrum of TOF (Figure 2). Pulmonary atresia may alternatively present with an intact ventricular septum, or in the setting of more complex anatomy (eg, transposition of great arteries, tricuspid atresia, etc). Under the umbrella of pulmonary atresia, there is significant variability in the

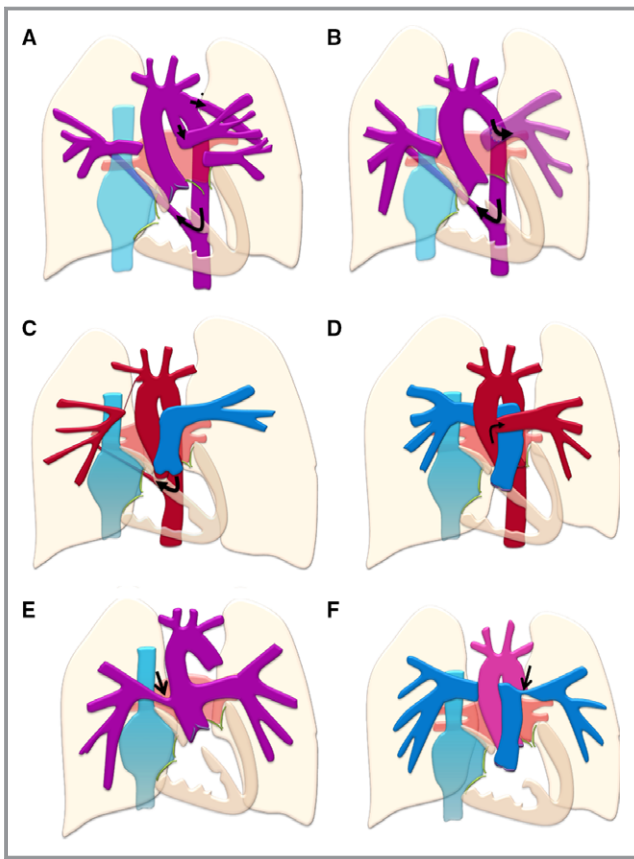


Figure 1. Schematic examples of segmental pulmonary hypertension. In (A), complex pulmonary atresia, with nonconfluent pulmonary arteries supplied by a patent ductus arteriosus and major aortopulmonary collateral arteries (MAPCAs) from the descending aorta (arrows), is shown. In (B), the left pulmonary artery is supplied by a Potts shunt and the right by a MAPCA from the descending aorta (arrows). Potts (descending aorta to left pulmonary artery) and Waterston (ascending aorta to right pulmonary artery) shunts are difficult to size and are therefore more likely to cause pressure and volume overload of the lung segments supplied, over time leading to the development of segmental pulmonary hypertension. In (C), unilateral absence of right pulmonary artery or isolated right pulmonary artery of ductal origin. There is a small outpouching of the innominate artery and a ductal remnant to the isolated pulmonary artery. The latter is supplied by a large MAPCA from the descending aorta (arrow), which may cause pulmonary hypertension (PH) to develop in the right lung. Pulmonary hypertension may also develop in the left lung only. In (D), hemitruncus arteriosus, with the left pulmonary artery arising from the hemitruncus (arrow) and the right from the main pulmonary artery in direct communication with the right ventricle. Only the left lung is hypertensive. In (E), common arterial trunk with stenosis of the origin of the right pulmonary artery (arrow) is shown. In this case, only the left lung is hypertensive. In (F), there is a large ventricular septal defect (VSD), and stenosis of the origin of the left pulmonary artery (arrow). In this condition, shunting through the nonrestrictive VSD is likely to cause distal PH and pulmonary vascular disease in the right, but not the left lung. Right-to-left shunting may be caused by right heart remodeling as a result of the combination of proximal left branch PA stenosis and distal right pulmonary vascular disease (PH).

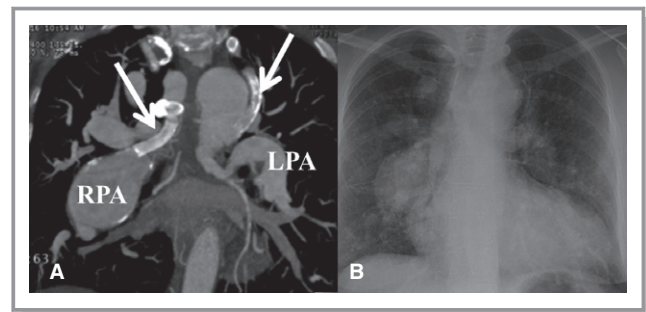


Figure 2. Tetralogy of Fallot with complex pulmonary atresia and previous bilateral Blalock Taussig shunts (A, arrows). The right pulmonary artery (RPA) is hypertensive and severely dilated, while the left pulmonary artery (LPA) is supplied by a relatively small collateral and is of normal caliber. This patient has segmental pulmonary hypertension, with pulmonary hypertension of various severities in different segments of the lung (eg, right mid and lower), while other segments are normotensive and may be hypoperfused. In (B), chest radiograph of the same patient shows a boot-shaped heart with inhomogeneous pulmonary vascular markings.

anatomy of the PAs. When branch PAs are of adequate size and confluent, it allows for an anatomic repair by implantation of a RV to PA conduit.⁶ Alternatively, when the branch PAs are hypoplastic, construction of a Blalock-Taussig or a central shunt may be needed to promote growth of the PAs to eventually allow conduit repair, with or without unifocalization.

In TOF with “complex” pulmonary atresia, the PAs are typically hypoplastic and have reduced bronchopulmonary segments; they may be nonconfluent and supplied by a PDA, or represent major systemic-to-pulmonary collateral arteries anatomically distinct from the PDA (also termed major aortopulmonary collateral arteries [MAPCAs] Figure 3).⁶ In extreme cases, the entire intrapericardial pulmonary arterial tree is absent and blood is supplied to the lungs by collateral arteries only. Some patients may be amenable to surgical repair.^{7–9} “Unifocalization” is a staged approach aimed at reconstructing the PAs and perfusing them by means of modified Blalock-Taussig shunts with the ipsilateral subclavian arteries, or with other shunts as dictated by specific PA anatomy. Thereafter, the reconstructed PAs can be connected to the RV with a RV-PA conduit, with subsequent closure of the VSD, as long as proximal PA pressure is low enough.

Patients with pulmonary atresia who do not undergo early operation or have only received a palliative intervention or partial unifocalization develop segmental PH as a result of large MAPCAs or palliative shunts (especially Waterston or Potts anastomoses, which are challenging to size) causing excessive flow and shear stress to certain, but not all, lung segments. Patients in whom unifocalization has been possible, but PA pressures are high, may receive an RV-PA conduit

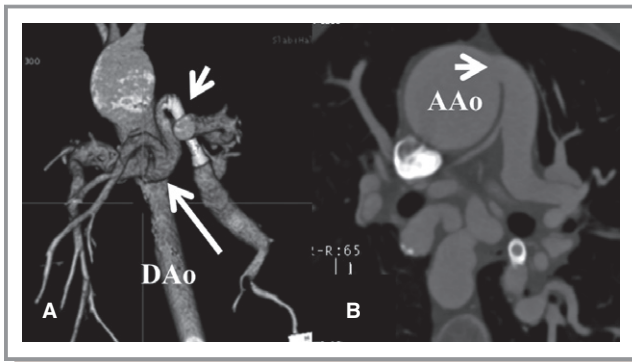


Figure 3. Computed tomography scan of a patient with tetralogy of Fallot and complex pulmonary atresia. In (A), major aortopulmonary collateral arteries (MAPCAs, arrow) arising from the descending aorta (DAo), some of which are large and may cause pulmonary hypertension in the areas supplied, while others are narrow and have required stenting to ensure adequate perfusion in the respective lung segments. In (B), a large MAPCA (arrow) arising from the ascending aorta (AAo) and supplying a hypertensive lung segment is seen. Numerous other MAPCAs are seen within the mediastinum. Ascending aortic dilation is apparent.

but the VSD is kept open (or closed using a valved patch) as a potential “relief valve” for the RV. Finally, even in patients with “successful” repair, residual or recurrent peripheral PA stenoses are not uncommon after unifocalization, and pulmonary vascular disease in segments previously supplied by large MAPCAs may result in segmental PH.

Unilateral Absence of PA or Isolated PA of Ductal Origin

Unilateral “absence” of a PA is very rare. The term “absent” PA is not accurate, as a hilar PA is typically present and supplied by a PDA or large collaterals but not the main PA, often leading to the development of PH in a single lung.^{10,11} Several authors have used the terms “isolated PA of ductal origin” or “unilateral ductal origin of a PA” to more accurately describe this condition. Strategies to rehabilitate the isolated PA have been reported.^{12–17}

Its prevalence as an isolated lesion is estimated at 1 in 200 000-to-300 000 adults,^{10,18–20} and 80% of reported cases involving the left PA have been associated with coexisting CHD, such as TOF or truncus arteriosus.^{10,19} In 2011, a review of the literature reported 352 cases of unilateral “absence” of pulmonary artery; two thirds (n=237) were associated with other CHD.²¹ PH is present in 44% of cases and, in conjunction with the underlying CHD, affects appropriate management and outcomes for these patients.^{18,19,22} PH may occur as a result of increased flow to the “healthy” lung, or in the “disconnected” lung supplied by large collaterals or a large PDA (Figure 4).^{22–24}

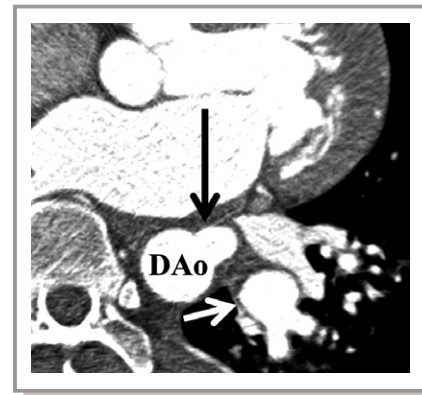


Figure 4. Anomalous origin of the left lower pulmonary artery (black arrow) from the descending aorta (DAo). The distal branches of the left lower pulmonary artery (white arrow) are dilated. There is segmental pulmonary hypertension limited in the left lower lung lobe.

Hemitruncus Arteriosus

Hemitruncus arteriosus refers to the abnormal origin of a single PA from the ascending aorta, with normal origin of the contralateral PA from the main PA; the latter is normally connected to the RV (Figure 5).^{5,6} Separate ventriculo-arterial junctions and separate aortic and pulmonary arterial valves mean that hemitruncus is a different entity from common arterial trunk (truncus arteriosus). The lung supplied by a normal-sized, unobstructed PA originating from the aorta is typically pressure and volume overloaded early in life and pulmonary vascular disease develops. Mortality is high in the first year of life (up to 70%) without timely repair.⁷ A small proportion of unrepaired patients do survive to adulthood and beyond, with segmental (eg, unilateral) PH.

Truncus Arteriosus With Stenosis or Hypoplasia of a Single PA or Branches

Truncus arteriosus is characterized by a common arterial trunk, giving rise to both the systemic and pulmonary circulation. The PAs originate from the arterial trunk in various patterns^{25,26} and the presence of normal-sized PAs results in bilateral PH, unless there is stenosis of the origin of 1 or both PAs (present in half of the patients). When branch pulmonary artery stenosis is severe, it may “protect” the respective lung from developing pulmonary vascular disease; segmental PH develops in the contralateral lung.^{26,27} Historically, patients without PA stenosis would often undergo banding of the PAs before definitive repair, while at the current time early, complete repair is the treatment of choice. A “slipped” PA band is not uncommon and has the same effect as congenital branch PA stenosis, protecting 1 but not both lungs. This may result in segmental PH.

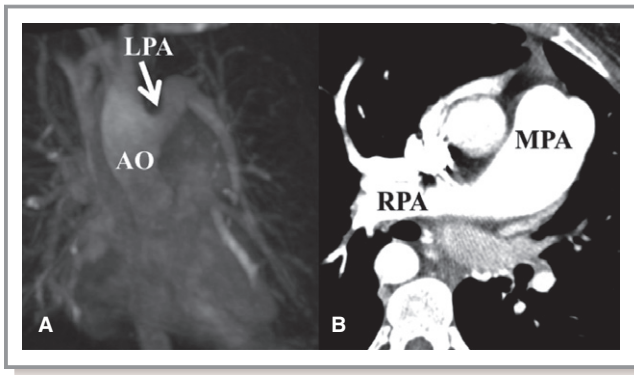


Figure 5. Hemitruncus arteriosus. In (A), the left pulmonary artery (LPA) is seen on cardiac magnetic resonance arising from the ascending aorta (AO). In (B), the right pulmonary artery (RPA) arises from the main pulmonary artery (MPA). In this situation, the left lung is hypertensive while the right is not, in the absence of associated CHD (eg, large VSD or PDA to the RPA). CHD indicates congenital heart disease; PDA, patent ductus arteriosus; VSD, ventricular septal defect.

Large Post-Tricuspid Defects With Peripheral Pulmonary Stenosis

Patients with large post-tricuspid shunts, such as a VSD, atrioventricular septal defect, PDA, or aortopulmonary window, are expected to develop pulmonary vascular disease in the absence of timely repair or effective PA banding. In unrepaired patients, or patients with a large residual post-tricuspid shunt, the presence of significant peripheral PA stenoses may “protect” part of the lung from the abnormal shear stress, resulting in segmental PH (Figure 6).

The remainder of this article will focus on the most common cause of segmental PH: TOF with complex pulmonary atresia.

Pathophysiology

Histology of the Pulmonary Circulation

The pathophysiology of segmental PH has not been well studied, but is likely to be the result of increased shear stress from excessive flow and pressure by large collaterals or abnormal origin of the PAs (similar to what is observed in patients with a large ventricular septal defect, patent ductus arteriosus, and common arterial trunk).²⁸ Moreover, hypoplasia of the pulmonary vascular bed is described in children. Thiene et al demonstrated that lung segments perfused by large, nonstenotic systemic collateral arteries in patients with pulmonary atresia had features of proliferative pulmonary vascular disease, including medial hypertrophy, intimal proliferation, and even plexiform lesions.²⁹ Different degrees of pulmonary vascular disease were detected in various lung

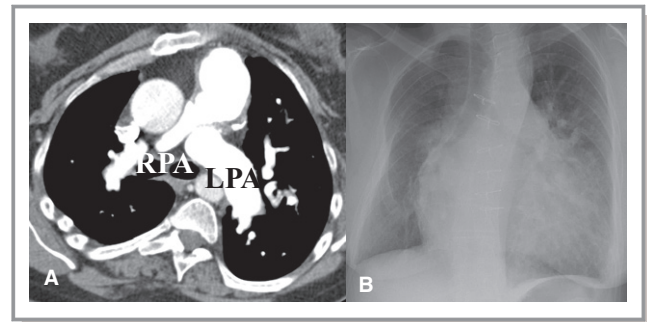


Figure 6. Tetralogy of Fallot and complex pulmonary atresia after conduit repair and closure of the ventricular septal defect, but with a significant residual shunt. In (A), there is significant pulmonary hypertension in the left lung with a dilated left pulmonary artery (LPA), while the right lung is “protected” by a stenosed right pulmonary artery (RPA). In (B), severe cardiomegaly with prominent pulmonary vascular marking in the hypertensive left lung are seen, but not in the right lung. Kyphoscoliosis, common in this group of patients, is also apparent and can independently impair pulmonary gas exchange and predispose towards pulmonary vascular remodeling in severe cases.

segments of a patient with multifocal PA supply. In the oldest child, who died at age 10 years, “obliterative” pulmonary vascular disease had developed. Haworth and Reid studied the lungs of neonates and children with pulmonary atresia, both those with intact ventricular septum and those with a VSD; they reported impaired lung development, with few and small pulmonary arteries with abnormally thin muscle coat.³⁰ Hence, the rise in segmental PVR in these patients may be the combined effect of pulmonary vascular disease and abnormal development of the pulmonary circulation, at both macroscopic and microscopic level. Understanding the pathophysiology of segmental PH is important for designing new treatment strategies for these patients.

Effects of Segmental PH on Pulmonary Physiology, Oxygen Tissue Delivery, and the Heart

In segmental PH, different areas of the lung receive different amounts of blood flow, at different pressures, and from different sources. Asymmetric perfusion results in ventilation/perfusion (V/Q) imbalance, which has been associated with adverse outcome in children with pulmonary atresia.³¹ V/Q mismatch results in a reduction in peripheral oxygen delivery at equivalent hemoglobin concentration and inefficient ventilation, imposing an additional workload on the heart and lungs. The coexistence of an intracardiac right-to-left shunt, with desaturated blood “bypassing” pulmonary gas exchange in the lung, causes further physiological dead space and V/Q mismatch, as does perfusion of the lung by partially

or fully saturated blood from the aorta, with little or no gas exchange occurring in such areas. Finally, gas exchange in patients with complex pulmonary atresia is also affected by the presence of hypertensive segments of the lung that are often adjacent to hypoperfused segments (supplied by small or stenosed collaterals).

There are, therefore, substantial differences in cardiac physiology in various types of segmental PH compared with other types of PH. The proposed classification of segmental PH reflects this and, specifically, the relation of the RV to the pulmonary circulation. In patients with complex pulmonary atresia or truncus arteriosus, the RV does not eject blood into the pulmonary circulation, and hence it is not directly affected by changes in pulmonary pressure and resistances. However, RV hypertrophy, dilatation, and dysfunction and tricuspid regurgitation can result from the large ventricular communication and resultant systemic RV pressures, ultimately leading to right heart failure independent of whether PH per se (ie, proximal PA pressure >25 mm Hg) is present. Moreover, systemic hypoxemia and chronic cyanosis affect all major organs, including the myocardium, producing an adverse effect on both the right and left ventricles. Indeed, the aorta receives a large quantity of blood, equal to the sum of the systemic and pulmonary blood flow. As patients age, both systemic ventricular and aortic dilation are common; aortic regurgitation can develop as a result of changes in aortic geometry. Some have expressed concern that pulmonary vasodilator medications (targeted PAH therapies) could further volume load the heart by significantly augmenting pulmonary blood flow. This has not been substantiated by the limited data available, with few patients followed for relatively short periods of time.³ Experience suggests, however, that life expectancy of patients with progressive symptoms related to complex pulmonary atresia may make long-term consequences of such therapies on cardiac structure and function less relevant to clinical practice.

For patients in whom the RV is directly connected to the entire pulmonary circulation, the effect of segmental PH on the RV is in addition to the load imposed by obstructive lesions (peripheral pulmonary stenosis, RV-PA conduits) themselves, the effects of previous cyanosis, surgical injury, and the burden of residual lesions (eg, a VSD). The interaction between the pulmonary circulation and the heart becomes even more complicated when the RV is “connected” to part rather than all of the pulmonary vascular tree; this merits further study, though disease rarity and heterogeneity present obstacles to systematic investigation. Finally, hemoptysis is not uncommon in pulmonary atresia, especially in patients with large hypertensive PAs. Understanding the anatomy of the PAs and collateral vessels is essential when considering embolization.

Assessment of Segmental PH in TOF With Pulmonary Atresia

Patients with complex pulmonary atresia in TOF are cyanosed at birth, because of obligatory mixing of oxygenated and deoxygenated blood within the aorta.⁶ Low or decreasing systemic oxygen saturations in complex pulmonary atresia may be related to PH or inadequate lung perfusion (eg, stenosis of collateral arteries or of a previously placed shunt). The first heart sound is normal but the second heart sound is typically single and loud, not because of PH, but because of the anterior positioning of the enlarged aorta below the chest wall. Continuous murmurs relating to the PDA or MAPCAs can be heard throughout the chest but become systolic and less prominent when PVR increases in the vascular bed distal to such vessels. Aortic regurgitation and stenosis may also develop in older patients, because of progressive aortic dilation.

The ECG usually shows signs of RV hypertrophy and right atrial dilatation. Echocardiography is essential when screening for PH, but is not sufficient for firmly establishing the diagnosis of segmental PH, and clearly less adequate for full definition of branch PA anatomy. It is important to remember that, in the absence of communication between the RV and PAs, neither estimates of RV pressure (using the tricuspid regurgitation velocity by Doppler) nor any property of the RV (eg, size or function) provide any insight into the state of the pulmonary circulation. However, Doppler can be used to interrogate flow through collateral vessels or surgical shunts, providing rough estimates of gradients between the aorta and the PAs. Continuous flow with a high peak velocity (>4 m/s in the presence of normal systemic pressures) can be taken as an indirect sign that no significant rise in pressure has occurred in the segment of lung fed by the interrogated shunt; a low peak velocity, in contrast, with a shunt that is mainly systolic suggests that PH and pulmonary vascular remodeling are likely.

Other noninvasive investigations can provide valuable information in the assessment of segmental PH in complex pulmonary atresia. The chest radiograph may show a “boot-shaped” heart, a combination of absent central PAs with an elevated apex because of RV hypertrophy, sometimes made more prominent by a right-sided aortic arch. The chest radiograph also provides information on the relative size of the central pulmonary arteries, which are often dilated when hypertensive, as well as the relative perfusion of various segments of the lung parenchyma (patchy and inhomogeneous pulmonary vascular markings with hypoperfused darker areas versus well-perfused brighter areas). Chest computed tomography pulmonary angiography provides more detailed information based on the same principles, and is a test of choice for obtaining anatomic information on the aorta, PAs,

and collateral arteries/shunts with excellent spatial resolution. In adult patients, a large MAPCA or PDA without stenosis invariably implies that the corresponding lung segment is hypertensive. Moreover, PA dilatation (with or without in situ thrombosis) is suggestive of PH. Cardiac magnetic resonance provides valuable information on cardiovascular anatomy, including the morphology and size of central PAs, the presence and function of large collateral arteries and shunts, as well ventricular function, aortic dimensions, and the function of the aortic valve.³²

Cardiac catheterization remains the criterion standard for assessing segmental PH but can be a long and laborious process, requiring administration of potentially large amounts of contrast medium and is best interpreted in conjunction with the noninvasive imaging data. A full hemodynamic study in patients with complex pulmonary atresia requires pump contrast injections in the aorta for the identification of MAPCAs and other shunts, followed by selective angiography and hemodynamic assessment of each vessel. Collateral vessels need to be adequately intubated to assess pressures in the respective distal pulmonary segments and the pressure gradients across the collaterals; some operators use coronary pressure wires for this purpose. Damage to important collateral vessels and shunts can have devastating consequences and cardiac catheterization should be undertaken in expert centers, only when essential and as a prelude to surgery or other intervention being considered for patients with symptomatic decline.

The anatomy of the pulmonary vascular tree influences the development of PH, response to therapy, and long-term outcome and is key in deciding when a patient can undergo biventricular repair. Patients with well-developed central pulmonary arteries provided by a ductus arteriosus have a significantly better prognosis and are more often amenable to primary repair with closure of the VSD and reconstruction of the right ventricular outflow tract by patch or conduit, compared with patients who are dependent on MAPCAs. Patients with more hypoplastic central pulmonary arteries may require palliation (eg, with a modified Blalock Taussig shunt) before proceeding to repair. In patients with MAPCAs, the number, size, and distribution of collateral arteries can vary considerably and influence the development of PH. Hence, it is important to perform imaging of the vascular bed early in life to assess how many of the segments are perfused centrally, and carefully assess patients for biventricular repair. Moreover, there is a relation between the vascular bed available and PH, and extensive, unrestrictive collateral vessels, which can lead to congestive heart failure early in life, can eventually result in PH.

The interplay between flow and pressure in different lung segments makes calculation of PVR a key to a deep understanding of underlying pathophysiology. However, in

the presence of multifocal blood supply, calculation of PVR may be challenging (or impossible) and magnetic resonance imaging or quantitative nuclear perfusion imaging may be of help in assessing pulmonary blood flow. In the setting of a strictly unifocal pulmonary blood supply (eg, single large PDA or MAPCA with confluent PAs), central PAs should be entered with the catheter to estimate PVR. As previously stated, prior advanced imaging with cardiac magnetic resonance imaging or computed tomography can delineate the target vessels and guide the invasive cardiac catheterization.

Clinical Management of Segmental PH: Surgical, Interventional, and Medical Therapy

In children born with complex pulmonary atresia with a VSD, the aim is to create an adequate pulmonary artery tree supplied by the right ventricle and close the VSD. Biventricular repair can be achieved through unifocalization (when PAs are not confluent) and implantation of a RV-PA conduit, while in a minority of cases a Fontan-type palliation or other palliative procedures may be undertaken.^{33–35} In unrepaired adults, unifocalization is often not feasible, and the presence of segmental PH precludes complete repair. A challenge is to ensure the lung segments are neither hypoperfused (excessive stenosis) nor hyperperfused (unrestrictive flow via large collaterals). Palliative shunts or dilatation +/- stenting of existing but stenosed MAPCAs or surgical shunts can be undertaken in symptomatic patients who present with hypoperfused lung segments.^{31,36,37} Experience is paramount, given the risks of immediate or delayed “reperfusion” pulmonary edema, hemoptysis, or other potentially catastrophic outcomes of injudicious interventions.

There are few reports on the effects of PAH medications (advanced therapies) in segmental PH. A multicenter study by Schuurin et al on 7 patients with segmental PH caused by pulmonary atresia reported a significant improvement in functional class and exercise tolerance (6-minute walk test distance improved by 62 m) with the endothelin-receptor antagonist bosentan.³ Another observational study by Lim et al on 5 adult patients with complex pulmonary atresia or severe pulmonary stenosis and MAPCAs treated with the phosphodiesterase-type 5 inhibitor sildenafil reported this therapy to be well tolerated in 4 of 5 patients, with a good clinical response to treatment in those patients.³⁸ Yamamura et al presented 2 children with segmental PH after pulmonary atresia treated with bosentan, with an improvement in symptoms, hemodynamics, and brain natriuretic peptide concentration.³⁹ Yasuhara and Yamagishi presented 3 patients who were likely to have segmental PH.⁴⁰ A pediatric patient developed PH after repair of pulmonary atresia (unifocalization). PA pressure improved through percutaneous treatment of peripheral pulmonary stenosis and combination

medical PAH therapy. An adult with unrepaired TOF, severe pulmonary stenosis, hypoplastic PAs, and MAPCAs had raised (peripheral) PA pressures and was treated with an endothelin-receptor antagonist, with alleviation of symptoms of exercise intolerance and improvement in quality of life. A third case of an adult with TOF and a hypoplastic left PA repaired at the age of 5 years presented at 27 years with an occluded left PA and raised PA pressures on the right PA. Treatment with an endothelin-receptor antagonist led to worsening hypoxemia, which the authors attributed to exacerbated V/Q mismatch or volume overload. Apostolopoulou et al reported the use of PAH therapies in 3 adult patients with unrepaired TOF and pulmonary atresia. PAH treatment resulted in an improvement in functional class and no adverse effects.⁴¹

Thus, the effect of PAH therapy in patients with segmental PH remains a matter of debate. While some evidence suggests this approach may be promising, there have been cases where therapies were not tolerated.^{38,39,42} An increase in pulmonary blood flow may, theoretically, overload the left ventricle and this should be taken into account when considering PAH therapies in patients with established left ventricular dysfunction and/or aortic stenosis or regurgitation. Limitations in the assessment of PVR and the effect of peripheral pulmonary stenoses also present a challenge in identifying patients who may benefit the most from PAH therapies. The use of PAH-specific therapies has been reported in a few cases of unilateral absence of a pulmonary artery; however, the evidence is not strong enough to allow for firm recommendations.

To Which World Health Organization PH Group Does Segmental Pulmonary Hypertension Best Belong?

Segmental PH appears to share histological features with PAH (group 1). Yet it also overlaps with PH in patients with pulmonary arterial obstructions, including congenital branch pulmonary artery stenosis or chronic thromboembolic PH (group 4), in terms of both the heterogeneity of histologic changes and perfusion, along with the potential for structural intervention in a subset. Some types of group 5 PH, such as fibrosing mediastinitis or pulmonary arterial compression by tumors, may also present with segmental PH. Intimal proliferation has been described in hypertensive lung segments of young patients with pulmonary atresia, although most of the available data are in infants. While medial hypertrophy and intimal proliferation in hypertensive lung areas in pulmonary atresia resemble the changes seen in PAH (group 1), the conditions grouped under PAH share not only histological, but also clinical features and a similar response to therapy. Hence, at present, it may seem appropriate to classify segmental PH within group 5, multifactorial PH,

reinforcing the complexity and unique physiology of this condition, and its distinct anatomical and clinical features compared with chronic thromboembolic PH. However, inclusion within group 1 (PAH related to CHD) may have the merit of reminding physicians this is a CHD-related condition, with significant similarities in pathophysiology to other CHD-related PAH (eg, chronic cyanosis) and may help inclusion in future research. Despite notable similarities with other types of PH, including chronic thromboembolic PH, it is imperative to approach segmental PH as a separate entity and practice caution when extrapolating information from other conditions with regard to medical and interventional treatment.

Where Should Patients With Segmental PH Be Managed?

Segmental PH is a complex condition that encompasses a broad spectrum of CHD and, less commonly, acquired causes. Assessment and interpretation of pathophysiology requires tertiary expertise both in CHD and PH. Confirmation of segmental PH, assessment of hemodynamics, and clinical relevance in individual cases and potential benefits of interventional and/or PAH therapies remain challenging. Patients with segmental PH should be cared for in tertiary centers with expertise in both PH and CHD patients, complex noninvasive and invasive investigations, and multidisciplinary support in terms of imaging, catheter, and cardiac surgical interventions. A broad recommendation on the use of PAH therapies cannot be made at present given the lack of evidence, though anecdotal experience suggests these therapies may have a role and may be considered empirically on an individualized basis in patients with confirmed segmental PH. Because of significant heterogeneity, coupled with a small patient population, it is unlikely that adequately powered randomized controlled trials will ever be feasible. However, well-structured prospective registries with prespecified baseline and follow-up protocols may shed additional light on the natural and unnatural history, and optimal management of segmental PH.

Author Contributions

Dimopoulos drafted the manuscript. All authors have provided feedback and critically revised the manuscript and its intellectual content.

Disclosures

Dimopoulos has acted as a consultant and received unrestricted educational or research grants from Bayer UK, Pfizer, Actelion, and GSK. Diller has received educational/travel grants from Actelion and Pfizer, and has served on the

advisory boards of Actelion, Germany. Opatowsky has received research grants from Actelion and Roche Diagnostics and has consulted for Novartis. D'Alto has served on the advisory board of Actelion, Bayer, United Therapeutics, and GlaxoSmithKline. Gu has received research grants from Actelion. Giannakoulas has acted as a consultant and/or received unrestricted educational or research grants from Actelion, Bayer, MSD, GlaxoSmithKline, Lilly, Pfizer, and United Therapeutics. Budts received a research grant from Actelion. Veldtman received a single research support from United Therapeutics. Beghetti has served as a consultant and/or advisory board member for Actelion, Bayer, Eli Lilly, GlaxoSmithKline, Novartis, and Pfizer and has received investigator-initiated research funding from Actelion and Bayer. Gatzoulis has acted as a consultant and received unrestricted educational or research grants from Bayer UK, Pfizer, and Actelion. The remaining authors have no disclosures to report.

References

- Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, Gomez Sanchez MA, Krishna Kumar R, Landzberg M, Machado RF, Olschewski H, Robbins IM, Souza R. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2013;62:D34–D41.
- Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M, Aboyans V, Vaz Carneiro A, Achenbach S, Agewall S, Allanore Y, Asteggiano R, Paolo Badano L, Albert Barberà J, Bouvaist H, Bueno H, Byrne RA, Carerj S, Castro G, Erol C, Falk V, Funck-Brentano C, Gorenflo M, Granton J, Jung B, Kiely DG, Kirchhof P, Kjellström B, Landmesser U, Lekakis J, Lionis C, Lip GYH, Orfanos SE, Park MH, Piepoli MF, Ponikowski P, Revel M-P, Rigau D, Rosenkranz S, Völler H, Luis Zamorano J. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS); endorsed by: association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2016;37:67–119.
- Schuuring MJ, Bouma BJ, Cordina R, Gatzoulis MA, Budts W, Mullen MP, Vis JC, Celermajer D, Mulder BJM. Treatment of segmental pulmonary artery hypertension in adults with congenital heart disease. *Int J Cardiol*. 2013;164:106–110.
- Tchervenkov CI, Roy N. Congenital Heart Surgery Nomenclature and Database Project: pulmonary atresia—ventricular septal defect. *Ann Thorac Surg*. 2000;69:S97–S105.
- Barbero-Marcial M. Classification of pulmonary atresia with ventricular septal defect. *Ann Thorac Surg*. 2001;72:316–317.
- Baker EJ, Anderson RH. Tetralogy of Fallot with pulmonary atresia. In: Anderson RH, Baker EJ, Penny D, Redington A, Rigby ML, Wernovsky G, eds. *Paediatric Cardiology*. 3rd ed. Philadelphia: Churchill Livingstone; 2010:775–794.
- Ashburn DA, Blackstone EH, Wells WJ, Jonas RA, Pigula FA, Manning PB, Lofland GK, Williams WG, McCrindle BW; Congenital Heart Surgeons Study members. Determinants of mortality and type of repair in neonates with pulmonary atresia and intact ventricular septum. *J Thorac Cardiovasc Surg*. 2004;127:1000–1007; discussion 1007–1008.
- Lightfoot NE, Coles JG, Dasmahapatra HK, Williams WG, Chin K, Trusler GA, Freedom RM. Analysis of survival in patients with pulmonary atresia and intact ventricular septum treated surgically. *Int J Cardiol*. 1989;24:159–164.
- Hoashi T, Kagisaki K, Kitano M, Kurosaki K, Shiraishi I, Yagihara T, Ichikawa H. Late clinical features of patients with pulmonary atresia or critical pulmonary stenosis with intact ventricular septum after biventricular repair. *Ann Thorac Surg*. 2012;94:833–841; discussion 841.
- Kruzliak P, Syamasundar RP, Novak M, Pechanova O, Kovacova G. Unilateral absence of pulmonary artery: pathophysiology, symptoms, diagnosis and current treatment. *Arch Cardiovasc Dis*. 2013;106:448–454.
- Gupta K, Livesay JJ, Lufschanowski R. Absent right pulmonary artery with coronary collaterals supplying the affected lung. *Circulation*. 2001;104:E12–E13.
- Mery CM, Molina KM, Krishnamurthy R, Fraser CD, Justino H. Pulmonary artery resuscitation for isolated ductal origin of a pulmonary artery. *J Thorac Cardiovasc Surg*. 2014;148:2235–2244.e1.
- Agrawal H, Petit CJ, Miro J, Miranda CD, Kenny D, Justino H. Contralateral pulmonary hypertension following resuscitation of unilateral ductal origin of a pulmonary artery: a multi-institutional review. *Pediatr Cardiol*. 2018;39:71–78.
- Al-Khaldi A, Tamimi O, Sallam M. Surgical experience in the rehabilitation and reimplantation of disconnected pulmonary arteries and its effectiveness in restoring pulmonary haemodynamics and function. *Eur J Cardiothorac Surg*. 2016;50:304–310.
- Miranda CD, Kenny D. Bilateral ductal stenting in a neonate with right isolated pulmonary artery of ductal origin and differential pulmonary vascular resistances. *Catheter Cardiovasc Interv*. 2016;87:1130–1134.
- Takatsuki S, Darst JR, Das BB, Fagan TE, Wolfe R, Ivy DD. Clinical manifestations and long-term follow-up in pediatric patients living at altitude with isolated pulmonary artery of ductal origin. *Pediatr Cardiol*. 2012;33:775–781.
- Bativalva SP, McElhinney DB, Pigula FA, Marshall AC. Isolated pulmonary artery arising from a duct: a single-center review of diagnostic and therapeutic strategies. *J Thorac Cardiovasc Surg*. 2014;148:2245–2252.
- Welch K, Hanley F, Johnston T, Cailes C, Shah MJ. Isolated unilateral absence of right proximal pulmonary artery: surgical repair and follow-up. *Ann Thorac Surg*. 2005;79:1399–1402.
- Ten Harkel ADJ, Blom NA, Ottenkamp J. Isolated unilateral absence of a pulmonary artery: a case report and review of the literature. *Chest*. 2002;122:1471–1477.
- Bouros D, Pare P, Panagou P, Tsimiris K, Siafakas N. The varied manifestation of pulmonary artery agenesis in adulthood. *Chest*. 1995;108:670–676.
- Bockeria LA, Makhachev OA, Khiriev TK, Abramyan MA. Congenital isolated unilateral absence of pulmonary artery and variants of collateral blood supply of the ipsilateral lung. *Interact Cardiovasc Thorac Surg*. 2011;12:509–510.
- Pool PE, Vogel JH, Blount SG. Congenital unilateral absence of a pulmonary artery. The importance of flow in pulmonary hypertension. *Am J Cardiol*. 1962;10:706–732.
- Haworth SG, de Leval M, Macartney FJ. Hypoperfusion and hyperperfusion in the immature lung. Pulmonary arterial development following ligation of the left pulmonary artery in the newborn pig. *J Thorac Cardiovasc Surg*. 1981;82:281–292.
- Haworth SG, McKenzie SA, Fitzpatrick ML. Alveolar development after ligation of left pulmonary artery in newborn pig: clinical relevance to unilateral pulmonary artery. *Thorax*. 1981;36:938–943.
- Collett RW, Edwards JE. Persistent truncus arteriosus; a classification according to anatomic types. *Surg Clin North Am*. 1949;29:1245–1270.
- Calder L, Van Praagh R, Van Praagh S, Sears WP, Corwin R, Levy A, Keith JD, Paul MH. Truncus arteriosus communis. Clinical, angiographic, and pathologic findings in 100 patients. *Am Heart J*. 1976;92:23–38.
- Van Praagh R, Van Praagh S. The anatomy of common aortopulmonary trunk (truncus arteriosus communis) and its embryologic implications. A study of 57 necropsy cases. *Am J Cardiol*. 1965;16:406–425.
- Rabinovitch M, Herrera-deLeon V, Castaneda AR, Reid L. Growth and development of the pulmonary vascular bed in patients with tetralogy of Fallot with or without pulmonary atresia. *Circulation*. 1981;64:1234–1249.
- Thiene G, Frescura C, Bini RM, Valente M, Gallucci V. Histology of pulmonary arterial supply in pulmonary atresia with ventricular septal defect. *Circulation*. 1979;60:1066–1074.
- Haworth SG, Reid L. Quantitative structural study of pulmonary circulation in the newborn with pulmonary atresia. *Thorax*. 1977;32:129–133.
- Dowdle SC, Human DG, Mann MD. Pulmonary ventilation and perfusion abnormalities and ventilation perfusion imbalance in children with pulmonary atresia or extreme tetralogy of Fallot. *J Nucl Med*. 1990;31:1276–1279.
- Prasad SK, Soukias N, Hornung T, Khan M, Pennell DJ, Gatzoulis MA, Mohiaddin RH. Role of magnetic resonance angiography in the diagnosis of major aortopulmonary collateral arteries and partial anomalous pulmonary venous drainage. *Circulation*. 2004;109:207–214.
- Rastelli GC, Ongley PA, Davis GD, Kirklin JW. Surgical repair for pulmonary valve atresia with coronary-pulmonary artery fistula: report of case. *Mayo Clin Proc*. 1965;40:521–527.
- Alfieri O, Blackstone EH, Kirklin JW, Pacifico AD, Barger LM. Surgical treatment of tetralogy of Fallot with pulmonary atresia. *J Thorac Cardiovasc Surg*. 1978;76:321–335.

35. Yagihara T, Yamamoto F, Nishigaki K, Matsuki O, Uemura H, Isizaka T, Takahashi O, Kamiya T, Kawashima Y. Unifocalization for pulmonary atresia with ventricular septal defect and major aortopulmonary collateral arteries. *J Thorac Cardiovasc Surg*. 1996;112:392–402.
36. Redington AN, Somerville J. Stenting of aortopulmonary collaterals in complex pulmonary atresia. *Circulation*. 1996;94:2479–2484.
37. Dinarevic S, Redington A, Rigby M, Shinebourne EA. Outcome of pulmonary atresia and ventricular septal defect during infancy. *Pediatr Cardiol*. 1995;16:276–282.
38. Lim ZS, Vettukattill JJ, Salmon AP, Veldtman GR. Sildenafil therapy in complex pulmonary atresia with pulmonary arterial hypertension. *Int J Cardiol*. 2008;129:339–343.
39. Yamamura K, Nagata H, Ikeda K, Ihara K, Hara T. Efficacy of bosentan therapy for segmental pulmonary artery hypertension due to major aortopulmonary collateral arteries in children. *Int J Cardiol*. 2012;161:e1–e3.
40. Yasuhara J, Yamagishi H. Pulmonary arterial hypertension associated with tetralogy of Fallot. *Int Heart J*. 2015;56(suppl):S17–S21.
41. Apostolopoulou SC, Vagenakis G, Rammos S. Pulmonary vasodilator therapy in tetralogy of Fallot with pulmonary atresia and major aortopulmonary collaterals: case series and review of literature. *Cardiol Young*. 2017;27:1861–1864.
42. Grant EK, Berger JT. Use of pulmonary hypertension medications in patients with tetralogy of Fallot with pulmonary atresia and multiple aortopulmonary collaterals. *Pediatr Cardiol*. 2016;37:304–312.

Key Words: congenital heart disease • pulmonary atresia
• pulmonary hypertension • segmental pulmonary hypertension
• truncus arteriosus