Curr Treat Options Cardio Med (2019) 21: 16
DOI 10.1007/s11936-019-0718-3

Pediatric and Congenital Heart Disease (G Singh, Section Editor)

Diagnosis and Pathophysiological Mechanisms of Group 3 Hypoxia-Induced Pulmonary Hypertension

Kel Vin Woo, MD, PhD[1,2]
David M. Ornitz, MD, PhD[2]
Gautam K. Singh, MD[1,*]

Address
[*,1]Department of Pediatrics, Washington University School of Medicine, One Children's place, Campus Box 8116-NWT, St. Louis, MO, 63132, USA
Email: singh_k@wustl.edu
[2]Department of Developmental Biology, Washington University School of Medicine, Saint Louis, MO, USA

Published online: 22 March 2019

This article is part of the Topical Collection on *Pediatric and Congenital Heart Disease*

Keywords Pulmonary hypertension · Hypoxia · Group 3 pulmonary hypertension · Echocardiography · Right ventricle · Fibroblast growth factors

Abstract

Purpose of review Group 3 hypoxia-induced pulmonary hypertension (PH) is an important and increasingly diagnosed condition in both the pediatric and adult population. The majority of pulmonary hypertension studies to date and all three classes of drug therapies were designed to focus on group 1 PH. There is a clear unmet medical need for understanding the molecular mechanisms of group 3 PH and a need for novel non-invasive methods of assessing PH in neonates.

Recent findings Several growth factors are expressed in patients and in animal models of group 3 PH and are thought to contribute to the pathophysiology of this disease. Here, we review some of the findings on the roles of vascular endothelial growth factor A (VEGFA), platelet-derived growth factor B (PDGFB), transforming growth factor-beta (TGFB1), and fibroblast growth factors (FGF) in PH. Additionally, we discuss novel uses of echocardiographic parameters in assessing right ventricular form and function.

Summary FGF2, TGFB, PDGFB, and VEGFA may serve as biomarkers in group 3 PH along with echocardiographic methods to diagnose and follow right ventricle function. FGFs and VEGFs may also function in the pathophysiology of group 3 PH.

Introduction

Pulmonary hypertension (PH) is a severe form of pulmonary vascular disease that results in death in up to two-thirds of affected patients within 5 years of diagnosis. PH is a progressive obliterative vasculopathy with multiple etiologies and high mortality. In response to pathologic stimuli, the vasculature often reactivates developmental signaling pathways as an adaptive response. For example, in PH, activated signaling mechanisms in endothelial cells increase intimal hyperplasia and fibrosis to accommodate high pulmonary vascular pressures. Endothelial cell dysfunction, excessive vascular remodeling, inflammation, and in situ thrombosis contribute to progressive elevation of pulmonary vascular resistance. The histopathology of PH is well documented, but the molecular mechanisms underlying the vascular remodeling are poorly understood. There are five WHO subtypes of PH. Group 1 pulmonary arterial hypertension (PAH) (idiopathic) is most common and group 3 PH (hypoxia induced) is the second most common type of PH.

Group 3 PH is primarily caused by alveolar hypoxia associated with lung immaturity and bronchopulmonary dysplasia (BPD), impaired control of breathing and alveolar hypoventilation disorders, chronic obstructive lung disease (COPD), interstitial lung disease, or high altitude [1, 2]. PH significantly increases the morbidity and mortality in both COPD and BPD patients. Up to half of preterm infants with BPD and PH die within 2 years of diagnosis [3], and 64% of adults with COPD and PH will die within 5 years [4].

Pathologic changes in endothelial cell function and vessel wall inflammation lead to pulmonary vascular remodeling, increased vascular resistance, decreased compliance, and gradual pulmonary vascular occlusion. Sustained increase in right heart afterload ultimately results in right heart failure. Current pharmacological treatments focused on vasodilation for symptomatic relief have limited effects on vascular remodeling. Furthermore, common therapies that are being used for PH worsen the outcome for group 3 PH patients [5]. A mechanistic understanding of the pulmonary vascular remodeling in group 3 PH is thus necessary to help identify non-invasive diagnostic tools for early detection of cardiopulmonary compromise, to develop effective therapies, to monitor treatment response, and to improve overall outcome.

Group 3 PH, primarily due to hypoxemia, includes patients with developmental lung disorders such as BPD [1]. Preterm birth affects more than 500,000 babies born in the USA each year, and BPD is the most common complication in preterm infants born before 29-week gestation [3]. Preterm birth is associated with arrested development of the pulmonary vasculature and alveolar simplification [6] leading to functional hypoxemia and the development of PH. The improved survival of the extremely preterm neonate has led to increased numbers of patients with BPD and increased PH and right heart failure, which occurs in 12–25% of infants with BPD [7•]. These infants have a 2-year mortality rate of 33–48% after PH diagnosis [3]. Despite the increasing recognition of group 3 PH in preterm infants with BPD, there is a scarcity of studies into the mechanisms underlying this disease.

COPD is a prevalent condition, affecting between 10 and 20% of the population, currently the fourth leading cause of mortality worldwide [8]. COPD encompasses two main conditions, chronic bronchitis and emphysema, characterized by persistent inflammation of the airways and widespread destruction of the alveolar walls. In fact, PH is a strong predictor of mortality in COPD, being a far stronger predictor of survival than the forced expiratory volume in 1 second measure [4]. Recent evidence suggests that 5–10% of patients with COPD are also diagnosed with PH, and these patients have an increased mortality rate [9].

Assessment of RV form and function, and pulmonary hemodynamics in group 3 hypoxia-induced pulmonary hypertension

The clinical course of group 3 PH and prognosis in infants and children are mainly determined by the form and function of the target organ, the right ventricle (RV). Long-term increases in pulmonary vascular resistance (PVR) and

pulmonary artery pressure (PAP) resulting from structural alterations and abnormal vasoreactivity of the pulmonary vasculature may lead to cardiac remodeling due to changes in geometry, structure, and function of the RV [10–12]. RV remodeling is dictated by many factors including severity of RV afterload caused by increased PVR, duration of the PH, neurohormonal activation, and altered gene expression [13]. The remodeling is orchestrated by modulation of the myofiber architecture and distribution and ventricle-specific anisotropy in the contractile pattern, particularly if these events occur during myocardial maturation in the early postnatal period. Conventional imaging methods, such as two-dimensional (2D) and Doppler echocardiography, are often qualitative, and they are not sufficiently sensitive in detecting changes in myofiber architecture and RV contractile function to provide robust prognostic information. Advances in cardiac imaging of the RV, including ultrasonic tissue characterization by integrated backscatter imaging (IBI), strain imaging, and flow dynamics imaging, provide quantitative information that often precedes conventional qualitative echocardiographic indicators of structural and functional changes in the RV.

In this section, we discuss the assessment of RV form, function, and hemodynamics in neonates, infants, and children with group 3 PH.

Assessment of RV form

RV myoarchitecture can be quantitatively evaluated by ultrasonic tissue characterization. There is a close relationship between measured ultrasonic parameters (attenuation, backscatter, speed of sound) and the inherent properties of myocardial tissue. Both the biochemical properties and the geometric properties (organization of myoskeleton) of the myocardium combine to produce the observed ultrasonic measures.

Studies have shown that ultrasonic tissue characterization has the ability to differentiate normal from abnormal myocardium in the RV. In patients with an intracardiac shunt leading to RV overload, integrated backscatter ultrasonography revealed interstitial and replacement fibrosis in the RV myocardium. This was consistent with histologic analysis, despite preserved systolic function in the early stages [14–20]. Studies have used tissue characterization measurements to detect differences in myocardial functional and textural properties in the presence of pressure and/or volume RV overload that preceeded the clinical manifestation of RV dysfunction and failure in patients with PH [20].

Assessment of RV function

Strain measures the percentage change in myocardial deformation, whereas its time derivative, strain rate, defines the rate of deformation of the myocardium over time. Strain rate is a load-independent global measure of ventricular systolic function and correlates closely with myocardial contractility [21]. RV myocardial strain in 2D can be measured by a novel echocardiographic method that measures myocardial deformation from continuous frame-by-frame tracking of the speckle pattern, a technique called speckle tracking eechocardiography (STE).

2D strain estimated by STE has been used to assess RV function in patients with PH [22]. RV strain and strain rate showed a close relationship with invasive pulmonary hemodynamics (PVR, mean PAP, and cardiac output), exercise capacity, and independently predicted functional classes of PH [23]. Furthermore, 2D strain and strain rate changed in proportion to the degree of increase

in PAP in patients with idiopathic PH [23] and were further changed in patients with concomitant RV failure [24]. Assessment of RV longitudinal systolic strain and strain rate by STE has been reported to independently predict future right-sided heart failure, clinical deterioration, and mortality in patients with PH [25, 26•]. In a prospective study in extremely low gestational age neonates (ELGANs) that aimed to discern the predictive and tracking sensitivity of 2D echo, we compared longitudinal global strain of the RV at 32 weeks postconceptional age between ELGANs who did and did not develop BPD at 36 weeks postconceptional age (supplemental flow via nasal cannula, continuous positive airway pressure, or mechanical ventilation, the National Institutes of Health consensus definition of moderate and severe bronchopulmonary dysplasia) [27, 28]. ELGANs who developed BPD at 36 weeks postconceptional age had lower RV longitudinal global strain at both 32 weeks ($P < 0.003$) and 36 weeks ($P < 0.05$) than those who did not develop BPD at 36 weeks postconceptional age (Fig. 1a, b).

Echocardiographic assessment of flow hemodynamic characteristics

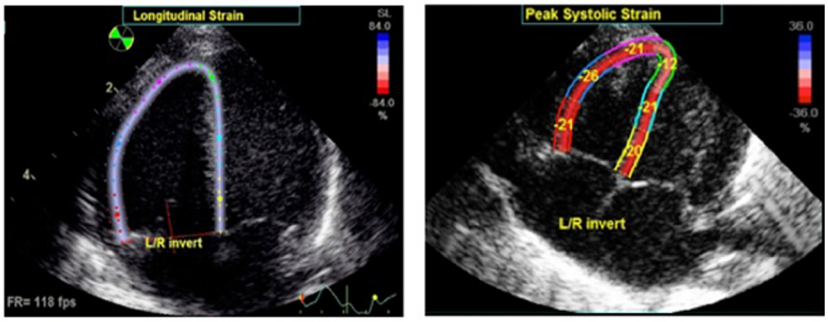
The heart is a dynamic organ that functions according to the principles of fluid dynamics. The structural form and mechanical function of the normal heart create time-varying and spatially complex flow patterns that are optimal for minimizing the energy required for normal function. Flow is immediately affected by changes in cardiac function and adaptation. Heart diseases and vascular alterations, including those caused by PH, have the potential to adversely alter these energy-efficient flow patterns. Therefore, analyzing the spatial and temporal distribution of blood flow in the heart and blood vessels may provide early diagnostic and prognostic information.

The methods that provide such information include crossed-beam approaches that use multiple transmitting and receiving transducers [29], vector flow mapping that combines the measured blood velocity along the ultrasonic beam axis with estimated orthogonal velocities obtained from the application of fundamental fluid dynamic principles [30], and methods that combine color Doppler measurements along with endocardial wall motion measurements and fundamental physical principles. Echocardiography-based particle image velocimetry (Echo-PIV) is a new method for quantifying blood flow dynamics [30–36]. The Echo-PIV method uses pairs of sequential image frames for calculating the direction and magnitude of contrast-enhanced blood flow. Tracking the displacement of contrast patterns in the second image, relative to the position of the patterns in the first image, provides a measure of the dynamics of blood flow. It is anticipated that emerging methods for assessing cardiac chamber blood flow may provide a means for recognizing early changes in flow dynamics that occur before the onset of clinical manifestations of cardiac dysfunction.

Molecular mechanisms associated with group 3 hypoxia-induced pulmonary hypertension

Research has led to drugs that have significantly decreased morbidity and prolonged life expectancy in patients with group 1 PAH. Unfortunately, none of these drugs show benefit to patients with group 3 PH [9]. In fact, recent clinical

a



b

Regional Strain	No CLD	Yes CLD	P value
Apex	-23 (2)	-18 (2)	< 0.001
Mid-ventricular	-24 (3)	-22 (1)	< 0.001
Base	-26 (1)	-25 (2)	< 0.001

c

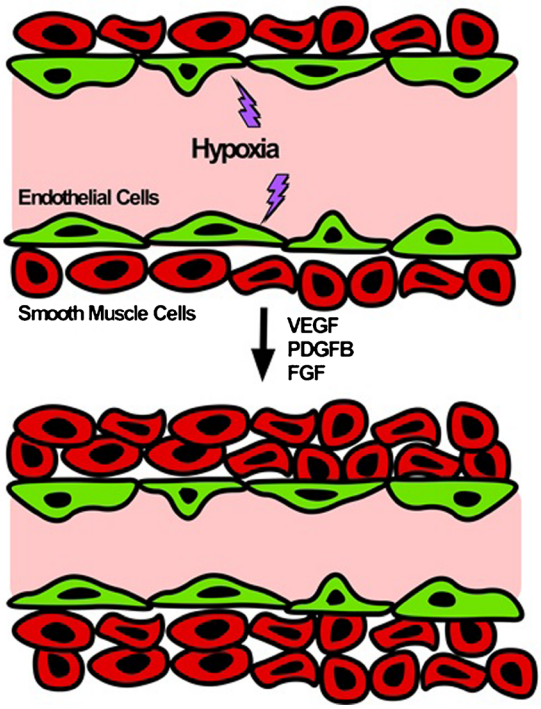


Fig. 1. Echocardiographic measure of strain and pathological markers and mediators of pulmonary hypertension. **a**, **b** RV regional strain in patients with vs. without chronic lung disease. Strain imaging of the right ventricle in an extremely low gestational age neonates using speckle-tracking echocardiography. The segmental strain is graphically presented by six different color-code curves and the global longitudinal strain by the white dotted curve. The peak of the average curve of all the segments (the dotted curve) was considered as peak global longitudinal strain (pGLS). AVC, aortic valve closure. **c** Summary role of VEGF, PDGFB, and FGF on PH.

trials of group 1–targeted therapies show, at best, no change in disease relief [37, 38], clinical worsening of disease [5], or increased risk of mortality [39] in group 3 PH patients. As such, understanding the pathophysiological mechanisms of

group 3 PH, finding new methods of monitoring disease, and identifying novel therapeutic targets is an unmet medical need. Here, we review the roles of some of the most commonly studied molecular mechanisms in group 3 hypoxia-induced PH (Fig. 1c).

TGFB1 in group 3 hypoxia-induced PH

Transforming growth factor-beta (TGFB1) regulates cellular growth, differentiation, and proliferation [40] and is a mediator of pulmonary development and cardiovascular disorders [41, 42]. TGF-β1 expression is correlated with physiologic alterations of the pulmonary vasculature and RV pressures and with hypoxia-induced factor-1 alpha (HIF1A) expression [43]. The TGFB1 signaling pathway contributes to the pathogenesis of PH [44, 45]. Liu et al. recently showed that rats exposed to hypoxia had increased expression levels of TGFB1 in their lungs when compared to normoxia controls [46]. This finding was associated with a decrease in expression of phosphatase and tensin homolog deleted on chromosome 10 (PTEN). TGFB1 promotes PH by increasing pulmonary artery smooth muscle cell survival and proliferation in a PTEN-dependent manner. Serum and lung tissue expression levels of TGFB1 are elevated and patients with idiopathic group 1 PH, along with expression of downstream mediators, activin receptor-like kinase-1 (ACVRL1), and endoglin (ENG) [47]. Interestingly, exogenous addition of TGFB1 to pulmonary artery smooth muscle cells resulted in production of fibroblast growth factor-2 (FGF2), platelet-derived growth factor β (PDGFB), and endothelin (END1). TGFB1 also increased smooth muscle proliferation in vitro in a SMAD-dependent manner. The TGFB1/ACVRL1/ENG signaling pathway stimulated growth factor and cytokine production in endothelial cells, thus mediating idiopathic group 1 PH in patients and hypoxia induced PH in mice [47].

VEGF and PDGFB in group 3 hypoxia-induced PH

HIF1A was first reported to induce vascular endothelial growth factor A (VEGFA) expression over 20 years ago [48, 49]. The role of VEGFA in many pathologic conditions including group 1 PAH is well investigated and reviewed [50]. Small ubiquitin-like modifier 1 (SUMO1) [51] and interleukin 33 (IL33) [52] augment the HIF1A/VEGFA/VEGFR2 signaling pathway. Both SUMO1 and IL33 augment the expression of HIF1A; additionally, SUMO1 binds the protein molecule in a sumoylation process [51]. The effect of VEGFA on group 3 PH came to the forefront as a new animal model for research [53, 54]. Expression of VEGFA, along with its receptor, VEGFR2, is increased in the lungs of rats challenged with chronic hypoxia [55, 56]. Overexpression of VEGFA in the lung protects against the development of chronic hypoxia-induced PH in rats, via increase in endothelial nitric oxide production [57]. Interestingly, loss of VEGFB expression had no effect on hypoxia-induced PH in mice, suggesting absence of a role for endogenous VEGFB [58]. However, overexpression of VEGFB resulted in a protective effect, thus suggesting a protective but redundant role of VEGFB in PH protection in the presence of VEGFA. Liang et al. reported that PDGFB augmented VEGFA expression via increasing Kruppel-like factor 4 (KLF4) promoter activity [59]. Additionally, PDGFB/PDGFRB and VEGFA/VEGFR2 interact in a biological complex augmenting hypoxia-induced endothelial cell proliferation.

FGF in group 3 hypoxia-induced PH

Recent studies highlight a major role for FGF signaling in the pathogenesis of PH. FGFs have been implicated in the proliferation, survival, and differentiation of many cell types, including endothelial cells [60–62]. Studies to date suggest that FGF signaling is involved in the pathogenesis of PH [63]. Expression of the FGF2 and FGF receptor tyrosine kinases, FGFR1 and FGFR2 [64, 65], is elevated in lung samples from patients with group 1 PH. In vivo rat models and in vitro studies suggest that FGF signaling worsens group 1 PH, and inhibition of its activity either with siRNA or the receptor tyrosine kinase inhibitor SUGEN5402 alleviates PAH [63, 65]. Endothelial cell cultures from patients with group 1, idiopathic pulmonary arterial hypertension, are resistant to apoptosis via up-regulation of antiapoptotic factors BCL2 and BCL2-like 1 (BCL2L1) in an FGF2 dependent manner [64].

FGF2 production is also markedly increased in preterm infants with BPD [66] and in patients with PH [67]. Mouse models of hypoxia-induced PH mimic human group 3 PH associated with hypoxia [68]. FGF2 production is increased in the presence of HIF1A in a positive feedback mechanism [69, 70]. Exposure of mice to chronic hypoxia commonly causes muscularization of previously non-muscularized vessels and medial thickening and stiffening of vessels [71], leading to elevated pulmonary artery pressure [63, 65]. FGF2 is also elevated in the mouse model of group 3 PH where mice are exposed to chronic hypoxia [47, 72], suggesting a role for FGF signaling in group 3 pathophysiology. However, the function of FGF signaling in endothelial and vascular smooth muscle cells, and downstream pathogenic and protective mechanisms is not known. It is also not known if there are differential effects of FGF signaling in group 1 vs. group 3 PH or in neonatal vs. adult PH.

Summary

The past 3 decades of scientific studies have focused on group 1 PAH. The 3 classes of drug therapies currently available were designed to treat patients in this group. While the underlying pathology for PH is pulmonary vascular wall thickening, the etiology is different and hence the mechanistic pathways to disease are likely different. Investigating new echocardiographic measures and discovering molecular mechanisms involved in group 3 hypoxia-induced PH will be important in the coming years. Additionally, several of these molecules may prove useful as serum biomarkers, that along with echocardiographic and ultrasound diagnostics will allow early detection of disease onset and progression, and for assessing therapeutic effectiveness.

Compliance with Ethical Standards

Conflict of Interest

Kel Vin Woo declares no potential conflicts of interest.
David M. Ornitz reports a grant from the NIH.
Gautam K. Singh is a section editor for *Current Treatment Options in Cardiovascular Medicine*.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance

1. Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix M, Denton CP, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2009;54(1 Suppl):S43–54.
2. Badesch DB, Raskob GE, Elliott CG, Krichman AM, Farber HW, Frost AE, et al. Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. Chest. 2010;137(2):376–87.
3. Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC, et al. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. Pediatrics. 2010;126(3):443–56.
4. Oswald-Mammosser M, Weitzenblum E, Quoix E, Moser G, Chaouat A, Charpentier C, et al. Prognostic factors in COPD patients receiving long-term oxygen therapy. Importance of pulmonary artery pressure. Chest. 1995;107(5):1193–8.
5. Raghu G, Behr J, Brown KK, Egan JJ, Kawut SM, Flaherty KR, et al. Treatment of idiopathic pulmonary fibrosis with ambrisentan: a parallel, randomized trial. Ann Intern Med. 2013;158(9):641–9.
6. Bhatt AJ, Pryhuber GS, Huyck H, Watkins RH, Metlay LA, Maniscalco WM. Disrupted pulmonary vasculature and decreased vascular endothelial growth factor, Flt-1, and TIE-2 in human infants dying with bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2001;164(10 Pt 1):1971–80.
7.• Mourani PM, Sontag MK, Younoszai A, Miller JI, Kinsella JP, Baker CD, et al. Early pulmonary vascular disease in preterm infants at risk for bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2015;191(1):87–95.

This is an important investigation that assessed the utility of echocardiography to identify preterm infants developing pulmonary vascular disease. Early echocardiograms may be useful in identifying patients at risk for BPD and PH.

8. Boucherat O, Morissette MC, Provencher S, Bonnet S, Maltais F. Bridging lung development with chronic obstructive pulmonary disease. Relevance of developmental pathways in chronic obstructive pulmonary disease pathogenesis. Am J Respir Crit Care Med. 2016;193(4):362–75.
9. Seeger W, Adir Y, Barberà JA, Champion H, Coghlan JG, Cottin V, et al. Pulmonary hypertension in chronic lung diseases. J Am Coll Cardiol. 2013;62(25 Suppl):D109–16.
10. Haddad F, Doyle R, Murphy DJ, Hunt SA. Right ventricular function in cardiovascular disease, part II: pathophysiology, clinical importance, and management of right ventricular failure. Circulation. 2008;117(13):1717–31.
11. Bogaard HJ, Natarajan R, Henderson SC, Long CS, Kraskauskas D, Smithson L, et al. Chronic pulmonary artery pressure elevation is insufficient to explain right heart failure. Circulation. 2009;120(20):1951–60.
12. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling—concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an international forum on cardiac remodeling. J Am Coll Cardiol. 2000;35(3):569–82.
13. Voelkel NF, Quaife RA, Leinwand LA, Barst RJ, McGoon MD, Meldrum DR, et al. Right ventricular function and failure: report of a National Heart, Lung, and Blood Institute working group on cellular and molecular mechanisms of right heart failure. Circulation. 2006;114(17):1883–91.
14. Hopkins WE, Waggoner AD, Gussak H. Quantitative ultrasonic tissue characterization of myocardium in cyanotic adults with an unrepaired congenital heart defect. Am J Cardiol. 1994;74(9):930–4.
15. Pacileo G, Calabro P, Limongelli G, Verrengia M, Di Salvo G, Russo GM, et al. Feasibility and usefulness of right ventricular ultrasonic tissue characterization with integrated backscatter in patients with unsuccessfully operatively "repaired" tetralogy of Fallot. Am J Cardiol. 2002;90(6):669–71.
16. Pacileo G, Limongelli G, Verrengia M, Gimeno J, Di Salvo G, Calabro R. Backscatter evaluation of myocardial functional and textural findings in children with right ventricular pressure and/or volume overload. Am J Cardiol. 2004;93(5):594–7.
17. Pacileo G, Limongelli G, Verrengia M, Miele T, Cesare G, Calabro P, et al. Impact of pulmonary regurgitation and age at surgical repair on textural and functional right ventricular myocardial properties in patients with tetralogy of Fallot. Ital Heart J. 2005;6(9):745–50.
18. Waggoner AD, Perez JE, Miller JG, Sobel BE. Differentiation of normal and ischemic right ventricular myocardium with quantitative two-dimensional integrated backscatter imaging. Ultrasound Med Biol. 1992;18(3):249–53.
19. Yildirim N, Saricam E, Ozbakir C, Bozboga S, Ocal A. Assessment of the relationship between functional capacity and right ventricular ultrasound tissue characterization by integrated backscatter in patients with isolated mitral stenosis. Int Heart J. 2007;48(1):87–96.

20. Yildirim N, Tekin NS, Tekin IO, Dogan S, Aydin M, Gursurer M, et al. Myocardial functional and textural findings of the right and left ventricles and their association with cellular adhesion molecules in Behcet's disease. Echocardiography. 2007;24(7):702–11.
21. Jamal F, Bergerot C, Argaud L, Loufouat J, Ovize M. Longitudinal strain quantitates regional right ventricular contractile function. Am J Physiol Heart Circ Physiol. 2003;285(6):H2842–7.
22. Chow PC, Liang XC, Cheung EW, Lam WW, Cheung YF. New two-dimensional global longitudinal strain and strain rate imaging for assessment of systemic right ventricular function. Heart. 2008;94(7):855–9.
23. Filusch A, Mereles D, Gruenig E, Buss S, Katus HA, Meyer FJ. Strain and strain rate echocardiography for evaluation of right ventricular dysfunction in patients with idiopathic pulmonary arterial hypertension. Clin Res Cardiol. 2010;99(8):491–8.
24. Pirat B, McCulloch ML, Zoghbi WA. Evaluation of global and regional right ventricular systolic function in patients with pulmonary hypertension using a novel speckle tracking method. Am J Cardiol. 2006;98(5):699–704.
25. Matias C, Isla LP, Vasconcelos M, Almeria C, Rodrigo JL, Serra V, et al. Speckle-tracking-derived strain and strain-rate analysis: a technique for the evaluation of early alterations in right ventricle systolic function in patients with systemic sclerosis and normal pulmonary artery pressure. J Cardiovasc Med (Hagerstown). 2009;10(2):129–34.
26.• Levy PT, El-Khuffash A, Patel MD, Breatnach CR, James AT, Sanchez AA, et al. Maturational patterns of systolic ventricular deformation mechanics by two-dimensional speckle-tracking echocardiography in preterm infants over the first year of age. J Am Soc Echocardiogr. 2017;30(7):685–98 e1.
This investigation uses 2DSTE in a large cohort of ELGAN from birth. BPD and PH negatively impact RV strain throughout the first year of life. Deformation imaging by 2DSTE may be used early to identify impending cardiovascular compromise, and guide early intervention.
27. Ambalavanan N, Walsh M, Bobashev G, Das A, Levine B, Carlo WA, et al. Intercenter differences in bronchopulmonary dysplasia or death among very low birth weight infants. Pediatrics. 2011;127(1):e106–16.
28. Levy PT, Holland MR, Sekarski TJ, Hamvas A, Singh GK. Feasibility and reproducibility of systolic right ventricular strain measurement by speckle-tracking echocardiography in premature infants. J Am Soc Echocardiogr. 2013;26(10):1201–13.
29. Dunmire B, Beach KW, Labs K, Plett M, Strandness DE Jr. Cross-beam vector Doppler ultrasound for angle-independent velocity measurements. Ultrasound Med Biol. 2000;26(8):1213–35.
30. Kim HB, Hertzberg JR, Shandas R. Echo PIV for flow field measurements in vivo. Biomed Sci Instrum. 2004;40:357–63.
31. Hong GR, Pedrizzetti G, Tonti G, Li P, Wei Z, Kim JK, et al. Characterization and quantification of vortex flow in the human left ventricle by contrast echocardiography using vector particle image velocimetry. JACC Cardiovasc Imaging. 2008;1(6):705–17.
32. Zhang F, Lanning C, Mazzaro L, Barker AJ, Gates PE, Strain WD, et al. In vitro and preliminary in vivo validation of echo particle image velocimetry in carotid vascular imaging. Ultrasound Med Biol. 2011;37(3):450–64.
33. Kheradvar A, Houle H, Pedrizzetti G, Tonti G, Belcik T, Ashraf M, et al. Echocardiographic particle image velocimetry: a novel technique for quantification of left ventricular blood vorticity pattern. J Am Soc Echocardiogr. 2010;23(1):86–94.
34. Sengupta PP, Burke R, Khandheria BK, Belohlavek M. Following the flow in chambers. Heart Fail Clin. 2008;4(3):325–32.
35. Sengupta PP, Khandheria BK, Korinek J, Jahangir A, Yoshifuku S, Milosevic I, et al. Left ventricular isovolumic flow sequence during sinus and paced rhythms: new insights from use of high-resolution Doppler and ultrasonic digital particle imaging velocimetry. J Am Coll Cardiol. 2007;49(8):899–908.
36. Faludi R, Szulik M, D'Hooge J, Herijgers P, Rademakers F, Pedrizzetti G, et al. Left ventricular flow patterns in healthy subjects and patients with prosthetic mitral valves: an in vivo study using echocardiographic particle image velocimetry. J Thorac Cardiovasc Surg. 2010;139(6):1501–10.
37. Idiopathic Pulmonary Fibrosis Clinical Research N, Zisman DA, Schwarz M, Anstrom KJ, Collard HR, Flaherty KR, et al. A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. N Engl J Med. 2010;363(7):620–8.
38. Jackson RM, Glassberg MK, Ramos CF, Bejarano PA, Butrous G, Gomez-Marin O. Sildenafil therapy and exercise tolerance in idiopathic pulmonary fibrosis. Lung. 2010;188(2):115–23.
39. Bayer terminates phase II study with riociguat in patients with pulmonary hypertension associated with idiopathic interstitial pneumonias [press release]. 2016.
40. Kajdaniuk D, Marek B, Borgiel-Marek H, Kos-Kudla B. Transforming growth factor beta1 (TGFbeta1) in physiology and pathology. Endokrynol Pol. 2013;64(5):384–96.
41. Bartram U, Speer CP. The role of transforming growth factor beta in lung development and disease. Chest. 2004;125(2):754–65.
42. Agrotis A, Kalinina N, Bobik A. Transforming growth factor-beta, cell signaling and cardiovascular disorders. Curr Vasc Pharmacol. 2005;3(1):55–61.
43. Jiang Y, Dai A, Li Q, Hu R. Hypoxia induces transforming growth factor-beta1 gene expression in the pulmonary artery of rats via hypoxia-inducible factor-1alpha. Acta Biochim Biophys Sin Shanghai. 2007;39(1):73–80.
44. Lu A, Zuo C, He Y, Chen G, Piao L, Zhang J, et al. EP3 receptor deficiency attenuates pulmonary hypertension through suppression of Rho/TGF-β1 signaling. J Clin Invest. 2015;125(3):1228–42.

45. Gilbane AJ, Derrett-Smith E, Trinder SL, Good RB, Pearce A, Denton CP, et al. Impaired bone morphogenetic protein receptor II signaling in a transforming growth factor-beta-dependent mouse model of pulmonary hypertension and in systemic sclerosis. Am J Respir Crit Care Med. 2015;191(6):665–77.
46. Liu Y, Cao Y, Sun S, Zhu J, Gao S, Pang J, et al. Transforming growth factor-beta1 upregulation triggers pulmonary artery smooth muscle cell proliferation and apoptosis imbalance in rats with hypoxic pulmonary hypertension via the PTEN/AKT pathways. Int J Biochem Cell Biol. 2016;77(Pt A):141–54.
47. Gore B, Izikki M, Mercier O, Dewachter L, Fadel E, Humbert M, et al. Key role of the endothelial TGF-β/ALK1/endoglin signaling pathway in humans and rodents pulmonary hypertension. PLoS One. 2014;9(6):e100310.
48. Namiki A, Brogi E, Kearney M, Kim EA, Wu T, Couffinhal T, et al. Hypoxia induces vascular endothelial growth factor in cultured human endothelial cells. J Biol Chem. 1995;270(52):31189–95.
49. Semenza GL, Wang GL. A nuclear factor induced by hypoxia via de novo protein synthesis binds to the human erythropoietin gene enhancer at a site required for transcriptional activation. Mol Cell Biol. 1992;12(12):5447–54.
50. Voelkel NF, Gomez-Arroyo J. The role of vascular endothelial growth factor in pulmonary arterial hypertension. The angiogenesis paradox. Am J Respir Cell Mol Biol. 2014;51(4):474–84.
51. Jiang Y, Wang J, Tian H, Li G, Zhu H, Liu L, et al. Increased SUMO-1 expression in response to hypoxia: interaction with HIF-1alpha in hypoxic pulmonary hypertension. Int J Mol Med. 2015;36(1):271–81.
52. Liu J, Wang W, Wang L, Chen S, Tian B, Huang K, et al. IL-33 initiates vascular remodelling in hypoxic pulmonary hypertension by up-regulating HIF-1alpha and VEGF expression in vascular endothelial cells. EBioMedicine. 2018;33:196–210.
53. Taraseviciene-Stewart L, Kasahara Y, Alger L, Hirth P, Mc Mahon G, Waltenberger J, et al. Inhibition of the VEGF receptor 2 combined with chronic hypoxia causes cell death-dependent pulmonary endothelial cell proliferation and severe pulmonary hypertension. FASEB J. 2001;15(2):427–38.
54. Nicolls MR, Mizuno S, Taraseviciene-Stewart L, Farkas L, Drake JI, Al Husseini A, et al. New models of pulmonary hypertension based on VEGF receptor blockade-induced endothelial cell apoptosis. Pulm Circ. 2012;2(4):434–42.
55. Christou H, Yoshida A, Arthur V, Morita T, Kourembanas S. Increased vascular endothelial growth factor production in the lungs of rats with hypoxia-induced pulmonary hypertension. Am J Respir Cell Mol Biol. 1998;18(6):768–76.
56. Tuder RM, Flook BE, Voelkel NF. Increased gene expression for VEGF and the VEGF receptors KDR/Flk and Flt in lungs exposed to acute or to chronic hypoxia. Modulation of gene expression by nitric oxide. J Clin Invest. 1995;95(4):1798–807.
57. Partovian C, Adnot S, Raffestin B, Louzier V, Levame M, Mavier IM, et al. Adenovirus-mediated lung vascular endothelial growth factor overexpression protects against hypoxic pulmonary hypertension in rats. Am J Respir Cell Mol Biol. 2000;23(6):762–71.
58. Louzier V, Raffestin B, Leroux A, Branellec D, Caillaud JM, Levame M, et al. Role of VEGF-B in the lung during development of chronic hypoxic pulmonary hypertension. Am J Physiol Lung Cell Mol Physiol. 2003;284(6):L926–37.
59. Liang S, Yu H, Chen X, Shen T, Cui Z, Si G, et al. PDGF-BB/KLF4/VEGF signaling axis in pulmonary artery endothelial cell angiogenesis. Cell Physiol Biochem. 2017;41(6):2333–49.
60. Fuks Z, Persaud RS, Alfieri A, McLoughlin M, Ehleiter D, Schwartz JL, et al. Basic fibroblast growth factor protects endothelial cells against radiation-induced programmed cell death in vitro and in vivo. Cancer Res. 1994;54(10):2582–90.
61. Wieder R, Wang H, Shirke S, Wang Q, Menzel T, Feirt N, et al. Low level expression of basic FGF upregulates Bcl-2 and delays apoptosis, but high intracellular levels are required to induce transformation in NIH 3T3 cells. Growth Factors. 1997;15(1):41–60.
62. König A, Menzel T, Lynen S, Wrazel L, Rosén A, Al-Katib A, et al. Basic fibroblast growth factor (bFGF) upregulates the expression of bcl-2 in B cell chronic lymphocytic leukemia cell lines resulting in delaying apoptosis. Leukemia. 1997;11(2):258–65.
63. Izikki M, Guignabert C, Fadel E, Humbert M, Tu L, Zadigue P, et al. Endothelial-derived FGF2 contributes to the progression of pulmonary hypertension in humans and rodents. J Clin Invest. 2009;119(3):512–23.
64. Tu L, Dewachter L, Gore B, Fadel E, Dartevelle P, Simonneau G, et al. Autocrine fibroblast growth factor-2 signaling contributes to altered endothelial phenotype in pulmonary hypertension. Am J Respir Cell Mol Biol. 2011;45(2):311–22.
65. Kim J, Kang Y, Kojima Y, Lighthouse JK, Hu X, Aldred MA, et al. An endothelial apelin-FGF link mediated by miR-424 and miR-503 is disrupted in pulmonary arterial hypertension. Nat Med. 2013;19(1):74–82.
66. Ambalavanan N, Novak ZE. Peptide growth factors in tracheal aspirates of mechanically ventilated preterm neonates. Pediatr Res. 2003;53(2):240–4.
67. Benisty JI, McLaughlin VV, Landzberg MJ, Rich JD, Newburger JW, Rich S, et al. Elevated basic fibroblast growth factor levels in patients with pulmonary arterial hypertension. Chest. 2004;126(4):1255–61.
68. Stenmark KR, Meyrick B, Galie N, Mooi WJ, McMurtry IF. Animal models of pulmonary arterial hypertension: the hope for etiological discovery and pharmacological cure. Am J Physiol Lung Cell Mol Physiol. 2009;297(6):L1013–32.

69. Conte C, Riant E, Toutain C, Pujol F, Arnal JF, Lenfant F, et al. FGF2 translationally induced by hypoxia is involved in negative and positive feedback loops with HIF-1alpha. PLoS One. 2008;3(8):e3078.
70. Schultz K, Fanburg BL, Beasley D. Hypoxia and hypoxia-inducible factor-1alpha promote growth factor-induced proliferation of human vascular smooth muscle cells. Am J Physiol Heart Circ Physiol. 2006;290(6):H2528–34.
71. Tuchscherer HA, Vanderpool RR, Chesler NC. Pulmonary vascular remodeling in isolated mouse lungs: effects on pulsatile pressure-flow relationships. J Biomech. 2007;40(5):993–1001.
72. Chang YT, Tseng CN, Tannenberg P, Eriksson L, Yuan K, de Jesus Perez VA, et al. Perlecan heparan sulfate deficiency impairs pulmonary vascular development and attenuates hypoxic pulmonary hypertension. Cardiovasc Res. 2015;107(1):20–31.

Publisher's Note