



2015

Pulmonary Rehabilitation and Exercise in Pulmonary Arterial Hypertension: An Underutilized Intervention

Sonu Sahni

Touro College of Osteopathic Medicine (New York), sonu.sahni@touro.edu

Barbara Capozzi

Touro College of Osteopathic Medicine (New York), barbara.capozzi@touro.edu

Asma Iftikhar

Vasiliki Sgouras

Marcin Ojrzanowski

See next page for additional authors

Follow this and additional works at: https://touro scholar.touro.edu/tcomny_pubs



Part of the [Osteopathic Medicine and Osteopathy Commons](#), [Pulmonology Commons](#), and the [Rehabilitation and Therapy Commons](#)

Recommended Citation

Sahni, S., Capozzi, B., Iftikhar, A., Sgouras, V., Ojrzanowski, M., & Talwar, A. (2015). Pulmonary rehabilitation and exercise in pulmonary arterial hypertension: An underutilized intervention. *Journal of Exercise Rehabilitation*, 11(2), 74-79.

This Article is brought to you for free and open access by the Touro College of Osteopathic Medicine (New York) at Touro Scholar. It has been accepted for inclusion in Touro College of Osteopathic Medicine (New York) Publications and Research by an authorized administrator of Touro Scholar. For more information, please contact touro.scholar@touro.edu.

Authors

Sonu Sahni, Barbara Capozzi, Asma Iftikhar, Vasiliki Sgouras, Marcin Ojrzanowski, and Arunabh Talwar

Pulmonary rehabilitation and exercise in pulmonary arterial hypertension: An underutilized intervention

Sonu Sahni¹, Barbara Capozzi², Asma Iftikhar¹, Vasiliki Sgouras³, Marcin Ojrzanowski⁴, Arunabh Talwar^{1,5,*}

¹North Shore - Long Island Jewish Health System, Department of Pulmonary, Critical Care and Sleep Medicine, New Hyde Park, NY, USA

²Touro College of Osteopathic Medicine, Department of Primary Care, New York, NY, USA

³Seton Hall University - School of Health and Medical Sciences, South Orange, NJ, USA

⁴W. Bieganski Hospital, Department of Cardiology, Łódź, Poland

⁵Hofstra North Shore - LIJ School of Medicine, Hofstra University, Hempstead, NY, USA

Pulmonary arterial hypertension (PAH) is a rare and devastating disease characterized by progressive increases in pulmonary arterial pressure and pulmonary vascular resistance which eventually leads to right ventricular failure and death. Early thought process was that exercise and increased physical activity may be detrimental to PAH patients however many small cohort trials have proven otherwise. In addition to the many pharmaceutical options, exercise and pulmonary rehabilitation have also been shown to increase exercise capacity as well as

various aspects of psychosomatic health. As pulmonary and exercise rehabilitation become more widely used as an adjuvant therapy patient outcomes improve and physicians should consider this in the therapeutic algorithm along with pharmacotherapy.

Keywords: Pulmonary arterial hypertension, Pulmonary rehabilitation, Six minute walk test, Exercise intolerance, Pulmonary hypertension, Health related quality of life

INTRODUCTION

Pulmonary hypertension is a rare and devastating disease characterized by progressive increases in pulmonary arterial pressure and pulmonary vascular resistance which eventually leads to right ventricular failure and death (Badesch et al., 2009; Farber and Loscalzo, 2004). It may due to various etiologies such as left heart disease, parenchymal lung disease, chronic thromboembolic disease, hematologic disorders or it may be idiopathic in nature (Table 1) (Simonneau et al., 2013) though the clinical picture of these patients is similar. Patients with all forms of pulmonary hypertension present with progressive dyspnea and increasing exercise intolerance. More specifically WHO Group I pulmonary arterial hypertension (PAH) is due to direct injury to the pulmonary vessels and vascular bed. At present there is no cure for PAH, however over the past decade targeted pharmaceutical options have become available. In addition to these pharmaceutical options, exer-

cise and pulmonary rehabilitation have also been shown to increase exercise capacity, WHO functional class, peak oxygen consumption and resting heart rate (Grunig et al., 2011; 2012a). It has also been seen that exercise may improve health related quality of life (HRQoL) (Chan et al., 2013), depression (Verma et al., 2014) and fatigue (Talwar et al., 2014). It is imperative that clinicians use pulmonary rehabilitation and exercise as an adjuvant therapy in the treatment of these patients as its benefits are clearly evident. This review will attempt to emphasize the importance of structured exercise training in the pulmonary hypertension population despite etiology and disease severity.

PULMONARY REHABILITATION

Over the last few decades pulmonary rehabilitation has advanced as a therapeutic option in patients of chronic respiratory disease. Evidence based medicine has determined that pulmonary

*Corresponding author: Arunabh Talwar

North Shore - Long Island Jewish Health System, Department of Pulmonary, Critical Care and Sleep Medicine, 410 Lakeville Rd. New Hyde Park, NY 11040, USA

Tel: +1-516-465-5400, Fax: +1-516-465-5454, E-mail: arunabh@nshs.edu

Received: February 14, 2015 / Accepted: April 8, 2015

Table 1. World Health Organization's classification of pulmonary hypertension (Simonneau et al., 2013)**Group I - Pulmonary Arterial hypertension (PAH)**

Idiopathic PAH
 Heritable PAH (BMPR2, ALK1, ENG, SMAD9, CAV1, KCNK3, Unknown)
 Drug and toxin induced
 Associated with (i) Connective tissue disease, (ii) HIV infection, (iii) Portal hypertension, (iv) Congenital heart disease, (v) Schistosomiasis
 Pulmonary veno-occlusive disease and/ or pulmonary capillary hemangiomatosis
 Persistent pulmonary hypertension of the newborn

Group II - Pulmonary hypertension due to left heart disease

Left ventricular systolic dysfunction
 Left ventricular diastolic dysfunction
 Valvular disease
 Congenital/ acquired left heart inflow/ outflow tract obstruction and congenital cardiomyopathies

Group III - Pulmonary hypertension due to lung diseases and/or hypoxia

Chronic obstructive pulmonary disease
 Interstitial lung disease
 Other pulmonary diseases with mixed restrictive and obstructive pattern
 Sleep-disordered breathing
 Alveolar hypoventilation disorders
 Chronic exposure to high altitudes
 Developmental lung disease

Group IV - Chronic thromboembolic pulmonary hypertension (CTEPH)**Group V - Pulmonary hypertension with unclear multifactorial mechanisms**

Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
 Metabolic disorders: glycogen storage disease, Gaucher's disease, hypothyroidism
 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental pulmonary hypertension

5th World Symposium on Pulmonary Hypertension, Nice, France 2013. BMPR, Bone Morphogenic Protein Receptor Type II; CAV1, Caveolin-1; ENG, Endoglin; HIV, Human Immunodeficiency Virus.

rehabilitation can reduce dyspnea, increase exercise tolerance and improve health related quality of life in all settings of chronic respiratory disease (Spruit et al., 2013). Pulmonary rehabilitation is defined as a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies, which include, but are not limited to, exercise training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence of health-enhancing behaviors (Spruit et al., 2013).

Use of exercise training and pulmonary rehabilitation in cardiopulmonary diseases such as congestive heart failure (CHF) and chronic obstructive pulmonary disease (COPD) have shown patient outcome improvement and are well described (Hambrecht et al., 1998; Ries et al., 2007). However, in the setting of pulmonary hypertension only small cohorts of studies exist. The use of exercise training and pulmonary rehabilitation in a pulmonary hypertension population is still underutilized though studies have shown its beneficial effect (de Man et al., 2009; Martinez-Quintana et al., 2010).

PULMONARY ARTERIAL HYPERTENSION AND EXERCISE IMPAIRMENT

Pulmonary arterial hypertension is characterized by a progressive increase in pulmonary vascular resistance, leading to right ventricular failure and eventual death (Simonneau et al., 2013). Prior to pharmacological intervention traditional therapies were utilized which included anticoagulants, diuretics, and supplemental oxygen. However, after the pathophysiologic process became well known disease-targeted therapies such as phosphodiesterase inhibitors, endothelin receptor antagonists and prostacyclins have become more widely used (Rubin, 2013). Combinations of these agents are used to decrease pulmonary vascular resistance, decrease pulmonary artery pressures and increase exercise tolerance (Pugh et al., 2013). Combination therapy with disease specific drugs has shown symptomatic relief as well as been shown to increase exercise capacity and possibly survival rate in pulmonary hypertension (Ghofrani et al., 2002; Hoeper et al., 2004). Though these medications address quantitative measures of pulmonary vasculature and hemodynamics, exercise capacity and quality of life continue to decline despite optimized treatment.

Exercise capacity is reduced in the setting of pulmonary hypertension which is associated with depression and anxiety disorders as demonstrated by Lowe et al. (2004). Until a better understanding of exercise training in the setting of pulmonary hypertension was established the early thought process was that exercise and increased physical activity may be detrimental to these patients and may actually increase pulmonary pressures expediting the proliferative process (Badesch et al., 2004).

The pathogenesis of pulmonary hypertension is multifactorial. WHO group I pulmonary hypertension, also referred to as pulmonary arterial hypertension is characterized by abnormalities initiating in the small arteries of the pulmonary vasculature, including enhanced cell proliferation and reduced apoptosis, endothelial dysfunction, thrombosis *in situ*, inflammation, and plexiform arteriopathy, leading to vascular remodeling and excessive vasoconstriction (McLaughlin et al., 2009). This may due to connective tissue diseases, congenital heart disease, HIV infection, portal hypertension, heritable or it may be idiopathic in nature. In the setting of PAH these changes cause resistance for the blood flowing through the pulmonary arteries. This leads to increased pulmonary artery pressures and increased pulmonary vascular resistance pressures eventually leading to right heart failure due to increased after load, decreased contractility, and reduced cardiac output (Waxman, 2012). The combination of reduced cardiac output and increased pulmonary vascular resistance creates a situation where exertion causes dyspnea and negatively affects quality of life.

Exertional dyspnea being a common symptom across the pulmonary hypertension population provides a method to assess disease severity and progress. Dyspnea may be measures subjectively by using instruments such as the Borg Dyspnea Scale and Medical Research Council Dyspnea Scale (Bestall et al., 1999; Borg, 1970). The severity of exertion is helpful to assess severity and prognosis in pulmonary hypertension. The 6-min walk test and the measure distance is used to assess exercise capacity in patients diagnosed with pulmonary disease and is used as the determinant and primary endpoint in many exercise training clinical trials (ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories, 2002). Exercise tolerance can also be measured using cardiopulmonary exercise testing (American Thoracic, Society/ American College of Chest Physicians, 2003).

CLINICAL TRIALS OF EXERCISE TRAINING AND PULMONARY REHABILITATION

Though early thought process advised against increased exer-

tion and exercise a change in thinking brought upon clinical trials of exercise respiratory training in the pulmonary hypertension population (Table 2). In Mereles et al., (2006) conducted the first prospective randomized study to evaluate the effects of exercise on chronically ill pulmonary hypertension patients, stable on medication. Thirty patients with either pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension were randomly assigned to either a control or training group. Primary end points were the change in 6-min walk distance from baseline to week 15 in the scores of the Short Form Health Survey quality-of-life questionnaire (SF-36). Secondary endpoints were also assessed. At week 15, patients in the primary and secondary training groups had an improved 6-min walking distance. Exercise training was shown to be well tolerated and improved scores of quality of life, WHO functional class and peak oxygen consumption. Systolic pulmonary artery pressure values at rest did not change significantly after 15 weeks of exercise and respiratory training (Mereles et al., 2006).

Though the ground work for exercise training in pulmonary hypertension was laid out, furthering testing was required. De Man et al. (2009) conducted a trial of exercise on only patients with WHO Group I PAH. Nineteen clinically stable PAH patients with moderate disease underwent exercise training program for 12 weeks in which maximal capacity endurance capacity and quadriceps function were assessed and serial quadriceps muscle biopsies were obtained. 6-min walk distance and peak exercise capacity did not change after training. However, endurance capacity improved significantly after training. Training also enhanced aerobic capacity of the quadriceps, by increasing capillarization (de Man et al., 2009).

A study by Fox et al. (2011) of 22 PAH or CTEPH patients demonstrated significant increase in 6 MWD as well as Peak VO_2 . The rehabilitation program consisted of 24 1-h sessions of exercise training/rehabilitation over the course of 12 weeks. Peak work rate during cardiopulmonary exercise test also increased in the rehabilitation group with borderline significance. Echocardiography and blood N-terminal pro-brain natriuretic peptide levels were unchanged. No adverse events occurred due to the rehabilitation program demonstrating safety.

With evidence of the positive benefits of exercise training in the setting of pulmonary hypertension further clinical trials were conducted. Grunig et al. (2011) demonstrated the benefits of exercise training in a connective tissue disease population with pulmonary hypertension (Grunig et al., 2012b). Patients with RHC confirmed connective tissue disease related pulmonary hypertension received in-hospital exercise training for 3 weeks which was con-

Table 2. Summary of exercise testing trial in the setting of pulmonary hypertension

Study	n	Study Design	Intervention	Duration of Exercise/ Rehab Program	Results
Mereles et al., 2006	30	RCT	Bicycle training, Walking, Dumbbell, Respiratory Training	3 week in hospital+ 12 weeks at home	Improvement in 6MWD, QOL scores, WHO FC, VO ₂ (peak +AT) and workload. No change in SPAP; No SAE
De Man et al., 2009	19	Non-randomized single group	Bicycle Training, Quadriceps stretch and endurance	12 weeks in rehabilitation center	Stable 6MWD, peak exercise capacity. Increased muscle strength, capillaries in muscle, oxidative enzyme activity.
Chan et al., 2013	23	RCT	Treadmill walking only for 30-45 min.	10 weeks 24-30 session in rehabilitation facility	Increase in 6MWD, QOL scores, Time to exercise intolerance, Peak work rate; No SAE
Fox et al., 2010	22	NRCT	1 hr. per session, aerobic interval training, bicycle, treadmill, walking, step climbing; resistance training.	12 weeks in outpatient rehabilitation center	Increase in 6MWD, Peak VO ₂ , Peak WR. BNP, SPAP and CO remained the same; No SAE
Grunig et al., 2011	58	NRCT single group	Daily bicycle training, dumbbell training, respiratory training	3 weeks in hospital, 12 week at home	Increased 6MWD, QOL scores, WHO FC, Peak VO ₂ , Maximum workload and decreased resting HR; No SAE
Grunig et al., 2012	183	NRCT single group	Daily interval bicycle training, walking, dumbbell training, mental training, home	3 weeks in hospital, 12 week at home	Increased 6MWD, QOL scores, WHO FC, Peak VO ₂ ; Decreased resting heart rate, and SPAP; No SAE
Grunig et al., 2012	21	NRCT single group	Daily interval bicycle training, walking, dumbbell training, mental training, home training	3 weeks in hospital, 12 week at home	Increased 6MWD, QOL scores, WHO FC, Peak VO ₂ , Maximum workload increased O ₂ SPAP; Survival at 2 yr-100%, 3 yr 73%

RCT, Randomized Controlled Trial; 6MWD, 6-min walk distance; QOL, Quality of life; WHO-FC, World Health Organization Functional Class; SAE, Serious Adverse Events; NRCT, Non-Randomized Control Trial; HR, Heart Rate; BNP, Brain Natriuretic Peptide; SPAP, Systolic Pulmonary Artery Pressure.

tinued for another 12 weeks at home. Patients improved the mean distance walked in 6 min, resting heart rate, peak oxygen consumption, and oxygen saturation. In addition systolic pulmonary artery pressure, and diastolic systemic blood pressure improved significantly after 3 weeks of exercise training. The 1- and 2-yr overall-survival rates were found to be 100%, the 3-yr survival rate 73% (Grunig et al., 2012a).

Another study by Grunig et al. (2011) aimed to assess disease progression and survival in patients with severe chronic pulmonary hypertension. Fifty eight patients with severe pulmonary hypertension on stable medication received exercise and respiratory training in hospital for 3 weeks which was later continued at home. They were prospectively followed for 24 ± 12 months. Primary endpoints were time to clinical worsening and survival. Adverse events and changes in the 6-min walking test, QoL, WHO functional class and gas exchange were secondary endpoints and were evaluated at baseline and at weeks 3 and 15. The results showed that all patients tolerated the exercise training well without any severe adverse events. In week 15, 6-min walking test results were significantly improved compared to baseline as well as quality of life scores, WHO functional class, peak oxygen consumption, heart rate at rest and maximal workload. Survival at 1 and 2 yr was 100 and 95%, respectively (Grunig et al., 2011).

Fifteen events occurred during the follow-up. It was concluded that exercise and respiratory training as add-on to medical treatment may improve exercise capacity and QoL, with a good long term safety profile.

NON PHYSICAL EFFECTS OF EXERCISE AND PULMONARY REHABILITATION

As pulmonary hypertension's most debilitating manifestation is exercise intolerance most trials focus on improvement in this characteristic as well as hemodynamics. However, in addition to physical improvement, there is a great deal of improvement in aspects of psychosomatic domains. It is well known that patients with pulmonary hypertension experience depression (Verma et al., 2014) and report increased levels of fatigue severity (Talwar et al., 2014). It is also well known that these patients have a severely impaired health related quality of life (Taichman et al., 2005). These aspects of psychosomatic medicine may also be addressed with the use of structured pulmonary rehabilitation and exercise programs in this population. A study by Kim et al. (2013) showed the effects that dyspnea has on depression and health related quality of life (HRQoL). Pulmonary rehabilitation programs have also showed improvement in fatigue severity as well as depression (Talwar et al.,

2014) which provide evidence of further benefits of such programs.

A more recent study by Chan et al. (2013) went ahead to determine the effects of intense treadmill exercise on cardio-respiratory function as well as quality of life in patients with pulmonary hypertension. Patients were randomized to a 10-week disease specific education only group or education/exercise combined group. The exercise program consisted of 24-30 sessions of treadmill walking for 30-45 min per session. Outcome variables included changes in 6-min walk test (6 MWT) distance, time to exercise intolerance, peak work rate from a cardiopulmonary treadmill test, and quality-of-life measures, including the SF-36 and Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) (Chan et al., 2013). The results following 10 weeks of intervention, demonstrated an improvement in 6 MWT distance, increased time to exercise intolerance, and peak WR. Additionally, the exercise group showed increased quality of life score according to the SF-36 as well as the CAMPHOR scale (Chan et al., 2013).

CONCLUSIONS

Pharmacotherapy for pulmonary arterial hypertension has advanced over the past decade and has provided clinicians with a disease specific approach which has led to the improvement in prognosis of PAH patients. However, patients continue to experience significant exertional symptoms accompanied by reduced functional capacity and diminished health-related quality of life. From the trials that have been conducted, the evidence supports the benefits and safety of exercise training and rehabilitation programs in the pulmonary hypertension populations. Initial exercise training and pulmonary rehabilitation programs were assessed in a stable, treated, systolic heart failure, and COPD and showed improved functional capacity and reduced exercise intolerance, symptoms of dyspnea, and fatigue.

Trials conducted in a pulmonary hypertension population showed improvement in exercise endurance and muscle strength as well as quality of life with the implementation of exercise training and cardiopulmonary rehabilitation as part of their medical care without a good safety profile. In conjunction with pharmacotherapy all patients with confirmed pulmonary arterial hypertension should be treated with a pulmonary rehabilitation and exercise training program.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was re-

ported.

REFERENCES

- American Thoracic Society/American College of Chest P. ATS/ACCP Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003;167(2):211-277.
- ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002;166(1):111-117.
- Badesch DB, Abman SH, Ahearn GS, Barst RJ, McCrory DC, Simonneau G, McLaughlin VV; American College of Chest Physicians. Medical therapy for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest* 2004;126(1 Suppl):35S-62S.
- Badesch DB, Champion HC, Sanchez MA, Hoeper MM, Loyd JE, Manes A, McGoon M, Naeije R, Olschewski H, Oudiz RJ, Torbicki A. Diagnosis and assessment of pulmonary arterial hypertension. *J Am Coll Cardiol* 2009;54(1 Suppl):S55-S66.
- Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* 1999;54(7):581-586.
- Borg G. Perceived exertion as an indicator of somatic stress. *Scand J Rehabil Med* 1970;2(2):92-98.
- Chan L, Chin LM, Kennedy M, Woolstenhulme JG, Nathan SD, Weinstein AA, Connors G, Weir NA, Drinkard B, Lamberti J, Keyser RE. Benefits of intensive treadmill exercise training on cardiorespiratory function and quality of life in patients with pulmonary hypertension. *Chest* 2013;143(2):333-343.
- de Man FS, Handoko ML, Groepenhoff H, van 't Hul AJ, Abbink J, Koppers RJ, Grotjohan HP, Twisk JW, Bogaard HJ, Boonstra A, Postmus PE, Westerhof N, van der Laarse WJ, Vonk-Noordegraaf A. Effects of exercise training in patients with idiopathic pulmonary arterial hypertension. *Eur Respir J* 2009;34(3):669-675.
- Farber HW, Loscalzo J. Pulmonary arterial hypertension. *N Engl J Med* 2004;351(16):1655-1665.
- Fox BD, Kassirer M, Weiss I, Raviv Y, Peled N, Shitrit D, Kramer MR. Ambulatory rehabilitation improves exercise capacity in patients with pulmonary hypertension. *J Card Fail* 2011;17(3):196-200.
- Ghofrani HA, Wiedemann R, Rose F, Olschewski H, Schermuly RT, Weissmann N, Seeger W, Grimminger F. Combination therapy with oral sildenafil and inhaled iloprost for severe pulmonary hypertension. *Ann Intern Med* 2002;136(7):515-522.
- Grunig E, Ehlken N, Ghofrani A, Staehler G, Meyer FJ, Juenger J, Opitz CF, Klose H, Wilkens H, Rosenkranz S, Olschewski H, Halank M. Ef-

- fect of exercise and respiratory training on clinical progression and survival in patients with severe chronic pulmonary hypertension. *Respiration* 2011;81(5):394-401.
- Grunig E, Lichtblau M, Ehlken N, Ghofrani HA, Reichenberger F, Staehler G, Halank M, Fischer C, Seyfarth HJ, Klose H, Meyer A, Sorichter S, Wilkens H, Rosenkranz S, Opitz C, Leuchte H, Karger G, Speich R, Nagel C. Safety and efficacy of exercise training in various forms of pulmonary hypertension. *Eur Respir J* 2012a;40(1):84-92.
- Grunig E, Maier F, Ehlken N, Fischer C, Lichtblau M, Blank N, Fiehn C, Stöckl F, Prange F, Staehler G, Reichenberger F, Tiede H, Halank M, Seyfarth HJ, Wagner S, Nagel C. Exercise training in pulmonary arterial hypertension associated with connective tissue diseases. *Arthritis Res Ther* 2012b;14(3):R148.
- Hambrecht R, Fiehn E, Weigl C, Gielen S, Hamann C, Kaiser R, Yu J, Adams V, Niebauer J, Schuler G. Regular physical exercise corrects endothelial dysfunction and improves exercise capacity in patients with chronic heart failure. *Circulation* 1998;98(24):2709-2715.
- Hoepfer MM, Faulenbach C, Golpon H, Winkler J, Welte T, Niedermeyer J. Combination therapy with bosentan and sildenafil in idiopathic pulmonary arterial hypertension. *Eur Respir J* 2004;24(6):1007-1010.
- Kim EJ, Verma S, Sahni S, Athanasiou K, Patel P, Kohn N, Talwar A. Dyspnea, depression and health related quality of life [HRQoL] in patients with pulmonary arterial hypertension [PAH]. *Chest* 2013;144(4 Meeting Abstracts):864A-A.
- Lowe B, Grafe K, Ufer C, Kroenke K, Grunig E, Herzog W, Borst MM. Anxiety and depression in patients with pulmonary hypertension. *Psychosom Med* 2004;66(6):831-836.
- Martinez-Quintana E, Miranda-Calderin G, Ugarte-Lopetegui A, Rodriguez-Gonzalez F. Rehabilitation program in adult congenital heart disease patients with pulmonary hypertension. *Congenit Heart Dis* 2010;5(1):44-50.
- McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, Mathier MA, McGoon MD, Park MH, Rosenson RS, Rubin LJ, Tapson VF, Varga J; American College of Cardiology Foundation Task Force on Expert Consensus Documents; American Heart Association; American College of Chest Physicians; American Thoracic Society, Inc; Pulmonary Hypertension Association. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. *J Am Coll Cardiol* 2009;53(17):1573-1619.
- Mereles D, Ehlken N, Kreuscher S, Ghofrani S, Hoepfer MM, Halank M, Meyer FJ, Karger G, Buss J, Juenger J, Holzapfel N, Opitz C, Winkler J, Herth FF, Wilkens H, Katus HA, Olschewski H, Grünig E. Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension. *Circulation* 2006;114(14):1482-1489.
- Pugh ME, Hemnes AR, Robbins IM. Combination therapy in pulmonary arterial hypertension. *Clin Chest Med* 2013;34(4):841-855.
- Ries AL, Bauldoff GS, Carlin BW, Casaburi R, Emery CF, Mahler DA, Make B, Rochester CL, Zuwallack R, Herrerias C. Pulmonary Rehabilitation: Joint ACCP/AACVPR Evidence-Based Clinical Practice Guidelines. *Chest* 2007;131(5 Suppl):4S-42S.
- Rubin LJ. Pulmonary hypertension: current management and future directions. *Handb Exp Pharmacol* 2013;218:551-555.
- 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(25 Suppl):D34-41.
- Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, Hill K, Holland AE, Lareau SC, Man WD, Pitta F, Sewell L, Raskin J, Bourbeau J, Crouch R, Franssen FM, Casaburi R, Vercoulen JH, Vogiatzis I, Gosselink R, Clini EM, Effing TW, Maltais F, van der Palen J, Troosters T, Janssen DJ, Collins E, Garcia-Aymerich J, Brooks D, Fahy BF, Puhan MA, Hoogendoorn M, Garrod R, Schols AM, Carlin B, Benzo R, Meek P, Morgan M, Rutten-van Mölken MP, Ries AL, Make B, Goldstein RS, Dowson CA, Brozek JL, Donner CF, Wouters EF; ATS/ERS Task Force on Pulmonary Rehabilitation. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med* 2013;188(8):e13-64.
- Taichman DB, Shin J, Hud L, Archer-Chicko C, Kaplan S, Sager JS, Gallop R, Christie J, Hansen-Flaschen J, Palevsky H. Health-related quality of life in patients with pulmonary arterial hypertension. *Respir Res* 2005;6:92.
- Talwar A, Sahni S, John S, Verma S, Cardenas-Garcia J, Kohn N. Effects of pulmonary rehabilitation on Fatigue Severity Scale in patients with lung disease. *Pneumonol Alergol Pol* 2014;82(6):534-540.
- Verma S, Cardenas-Garcia J, Mohapatra PR, Talwar A. Depression in pulmonary arterial hypertension and interstitial lung diseases. *N Am J Med Sci* 2014;6(6):240-249.
- Waxman AB. Exercise physiology and pulmonary arterial hypertension. *Prog Cardiovasc Dis* 2012;55(2):172-179.