Pulmonary Arterial Hypertension: A Serious Problem

Pulmonary arterial hypertension (PAH) is a serious disease with significant morbidity and mortality and no cure. In this article, Dr. Porhownik and Dr. Bshouty detail how early recognition of the disease and appropriate workup of possible underlying etiologies are essential.

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Pulmonary arterial hypertension (PAH) is a chronic, progressive disease of the pulmonary vascular system. Untreated, PAH leads to right ventricular failure and death in as little as a few months from the time of diagnosis. Vasoconstriction, pulmonary vessel wall remodeling and *in-situ* thrombosis are thought to be key contributors to this disease process. In spite of dramatic advances in understanding the pathophysiology and new treatment in the past few years, PAH remains a serious disease with significant morbidity and mortality and no cure. Early recognition of the disease and appropriate workup of possible underlying etiologies are essential.

Definition and Classification

PAH is present when mean pulmonary artery pressure (PAPm) exceeds 25 mmHg at rest or 30 mmHg with exercise, in association with a pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg and a calculated pulmonary vascular resistance (PVR) greater than 3 mm Hg/L/min (Wood units). The classification of pulmonary hypertension (PH) was revised at the World Health Organization (WHO) World Symposium in Venice in 2003,[1] and currently includes five categories:

1. PAH;
2. PH with left heart disease;
3. PH with lung diseases and/or hypoxemia
4. PH due to chronic thrombotic and/or embolic disease
5. Miscellaneous causes

PAH is further subclassified as:

- idiopathic (IPAH),
- familial (FPAH),
- associated with pulmonary veno-occlusive disease (PVOD) or pulmonary capillary hemangiomatosis (PCH),
- persistent pulmonary hypertension of the newborn (PPHN) and
- in association with conditions including:
  - collagen vascular diseases (CVD),
  - congenital heart disease (CHD),
  - portal hypertension,
  - HIV,
  - drugs,
  - toxins, *etc*.

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Epidemiology

PAH has an incidence of 2.4 cases per million people per year and a prevalence of 15 cases per million people. Women are more commonly affected, comprising 60% of cases. The mean age at diagnosis is 50 years with a wide range from second to ninth decade.[2] Forty per cent of cases are idiopathic, 4% are familial, 16% are associated with CVD, 12% CHD, 10% anorexigens and 18% are associated with other causes.

Pathophysiology

The pathophysiology of PAH is a complex interplay of multiple mediators and pathways. A combination of genetic predisposition and exposure to risk factors is thought to lead to the development of PAH. Increased activity has been shown of several aggravating mediators, including:

- endothelin-1,
- serotonin,
- thromboxane A2,
- angiopoietin-1,
- plasminogen activator inhibitor,
- clotting, growth and inflammation factors, as well as
- pathways of oxidant stress.

Simultaneously, decreased activity of potentially protective factors have been noted, such as:

- prostacyclin,
- prostacyclin synthase,
- nitric oxide,
- nitric oxide synthase,
- vasoactive intestinal peptide and
- fibrinolysis.

Changes in these mediators result in vasoconstriction, pulmonary vasculature remodeling and *in-situ* thrombosis, causing increased pulmonary vascular resistance. Some of these molecular mechanisms have become targets of therapy.

Presentation

Symptoms and signs of PAH, at various stages of the disease, are best understood by viewing disease progression as persistent increases in pulmonary vascular resistance (PVR) (Figure 1). In the initial,

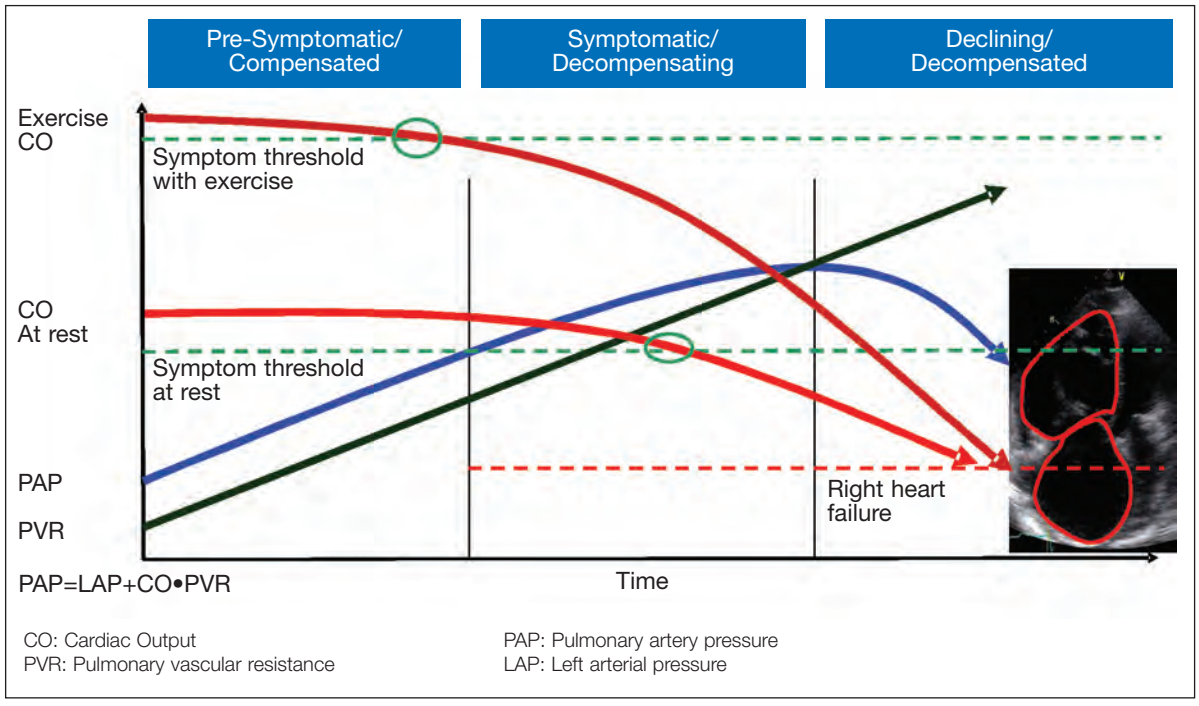

Figure 1. Progression of pulmonary arterial hypertension.

asymptomatic phase, cardiac output is maintained as PVR increases. Since patients in this stage experience either no symptoms or mild symptoms with exertion, annual screening of high risk patients is mandatory. In the symptomatic or decompensating phase, the exercise threshold at which patients experience symptoms starts to decline as cardiac output during exercise is no longer maintained against a continually increasing PVR. Patients note progressive dyspnea on exertion. They may also complain of:

- fatigue,
- palpitations,
- presyncope and
- chest pain.

The third phase of decline and decompensation marks a drastic fall in cardiac output and symptoms occur with lower levels of activity and eventually at rest. In end-stage disease, pulmonary artery pressures may begin to fall due to a severe drops in cardiac output as PVR continues to rise. Once the disease progresses to end-stage, patients have signs and symptoms of right heart failure, edema and ascites. Cardiovascular (CV) examination reveals a loud pulmonic component of S2, widely split S2, right ventricular S3, S4 and heave. Murmurs of tricuspid and pulmonic regurgitation may be heard. Jugular venous pressure waves are enlarged.

WHO Functional Classification is used to assess the clinical severity of PAH. Patients in Class I have no limitation of usual physical activity. Class II patients have mild limitations of usual physical activity, but no symptoms at rest. Class III patients have marked limitations of usual physical activity, but no symptoms at rest. Patients in Class IV are incapable of performing any physical activity, have symptoms at rest and may have right ventricular failure. This classification is important because it is used to guide treatment and is predictive of survival (see Treatment and Prognosis sections).

Vasodilator response, present in only 10% of patients, is clinically relevant as these patients have a better prognosis and can be treated with CCBs

Investigations

The diagnosis of PAH is confirmed by right heart catheterization. All other investigations are either suggestive or supportive. ECGs may show signs of right atrial enlargement, right ventricular enlargement and right ventricular strain patterns. Chest x-rays show signs of right atrial and ventricular enlargement and prominent pulmonary vasculature. In the absence of underlying lung disease, the only abnormality seen on pulmonary function tests is a reduction in diffusion capacity. A high resolution CT scan of the lungs can be used to assess the severity of the underlying lung disease. Infused CT scans may be ordered to rule out pulmonary embolism as a cause of elevated right-sided pressures.

Transthoracic doppler echocardiography is a useful, noninvasive screening test for pulmonary hypertension. Enlarged right-sided chambers and

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flattening or paradoxical movement of the interventricular septum may be seen. Tricuspid regurgitation allows an estimate of right ventricular systolic pressure. Ventilation-perfusion (V/Q) scans may be normal or show small peripheral subsegmental defects in perfusion. A pulmonary angiogram showing large central pulmonary arteries and pruning of the distal vessels, although diagnostic, is rarely performed.

As mentioned above, right heart catheterization is performed to confirm pulmonary hypertension. Standard measurements during right heart catheterization include:

- right atrial pressure,
- right ventricular pressure,
- PAP,
- PCWP,
- cardiac output and
- oxygen saturations.

During the procedure, a vasodilator challenge is performed to assess for vasoreactivity, or responsiveness of the vessels. A potent, short-acting vasodilator is administered under hemodynamic monitoring. Agents available for this test include:

- inhaled nitric oxide,
- intravenous epoprostenol and
- intravenous adenosine.

A significant vasodilator response is defined by satisfying all of the following criteria:

1. At least 10 mmHg drop in PAP m and a drop to a value ≤ 40 mmHg
2. Either an increase or no change in cardiac output
3. Vasodilator response, present in only 10% of patients, is clinically relevant as these patients have a better prognosis and can be treated with calcium channel blockers (CCB)

Treatment

Goals of therapy for PAH are to prevent clinical worsening and to improve:

- exercise capacity,
- functional class,
- hemodynamics and
- survival.

Until recently, the management of PAH was largely supportive. It consisted of oxygen supplementation, anticoagulation, diuretics and digoxin (controversial). Recently, significant advances in the treatment of PAH have shown encouraging outcomes. Four classes of medications have shown efficacy in the treatment of PAH:

- CCBs,
- endothelin receptor antagonists (ERAs),
- phosphodiesterase-5 (PDE-5) inhibitors and
- prostanoids.

These medications differ in their mechanisms of action, indications, routes of delivery and side-effect profiles.

Anticoagulation has been a part of the management of PAH based on inherent risk factors for venous thromboembolism, including:

- heart failure,
- sedentary lifestyle and
- thrombophilia.

However, studies of anticoagulation are lacking and no data specifically supports anticoagulation in patients with PAH. A systematic review of the literature by Johnson, *et al*[4] supports a treatment effect of warfarin, but the available evidence is considered insufficient for formal conclusions. A target international normalized ratio (INR) of 1.5 to 2.5 is usually recommended if not otherwise contraindicated.

Contraception is recommended in women of childbearing age since the stress of pregnancy and labour on the CV system is detrimental in pulmonary hypertension. Oral contraceptives are generally an acceptable method, unless the patient has chronic thromboembolic disease.

Patients who may benefit from CCBs are identified by a positive vasodilator challenge during right heart catheterization. The routine

use of CCBs as first-line therapy is no longer advised as it is rarely effective and potentially dangerous in patients who do not show a favourable response to vasodilator challenge. CCBs are effective in only a small subset (5% to 10%) of patients with PAH.

Three major pathways involved in pulmonary vasoconstriction and abnormal proliferation of smooth muscle cells are targeted in PAH therapy. The three pathways are:

- the prostacyclin pathway,
- the endothelin pathway and
- the nitric oxide pathway.

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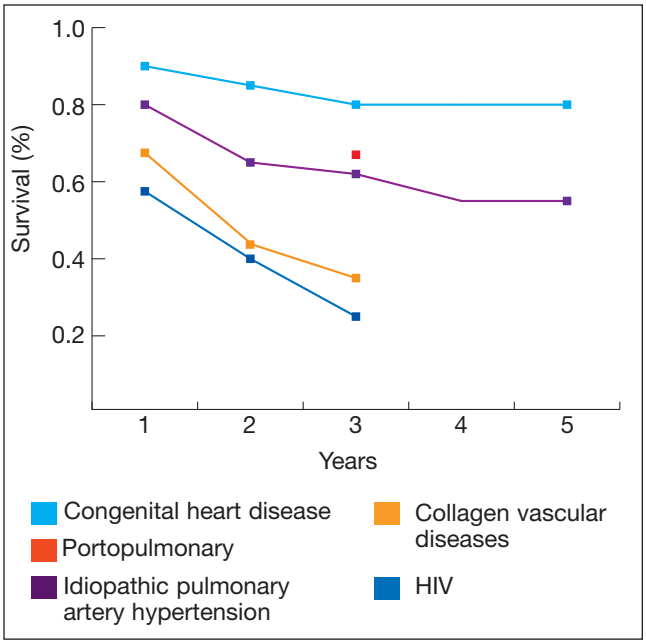

Figure 2. Survival in pulmonary arterial hypertension by diagnosis. Recreated from McLaughlin, *et al*.[9]

Prostanoids

Prostanoids (prostacyclin, prostaglandin I2) through cyclic adenosine monophosphate (AMP), induce vascular smooth muscle relaxation, inhibit smooth muscle proliferation and inhibit platelet aggregation. Epoprostenol, an intravenous prostacyclin, was the first Food and Drug Administration (FDA)-approved drug for PAH. It is the only medication for PAH that has shown a survival benefit in a prospective randomized placebo-controlled trial and is considered the most potent and efficacious treatment for PAH. However, of all of the therapies for PAH, epoprostenol is the most complex to administer, requiring a continuous intravenous (IV) infusion through a central line and daily preparation by the patient. The drug is also light-sensitive and unstable at room temperature, requiring protection from light and ice packs to keep it cold. The half-life of the medication is extremely short (two minutes to three minutes), making interruptions in drug administration potentially life-threatening. Side-effects of this treatment are twofold, first related to the drug itself and second related to the delivery system. Drug side effects include:

- jaw pain,
- diarrhea,
- arthralgias,
- nausea and
- systemic hypotension.

Side-effects because of the delivery system include:

- infection,
- thrombosis,
- pump malfunction and
- interruption of the infusion.

Epoprostenol is approved for patients with PAH in WHO functional classes III and IV.

Treprostinil is another prostacyclin analogue for the treatment of PAH. It can be administered either intravenously with a portable infusion pump (similar to

epoprostenol delivery), or subcutaneously using a mini pump (similar to insulin pumps). It has the benefit of a longer half life of approximately 4.5 hours. Local skin reactions are very common, with 83% of patients reporting infusion site reactions and 8% of patients discontinuing the medication due to these reactions.[5] The infusion site is typically rotated every few days to minimize local skin reactions. Other commonly reported side effects include:

- headache,
- diarrhea,
- nausea and
- rash.

Treprostinil has several advantages over epoprostenol, including:

- stability at room temperature,
- longer half-life making interruptions in administration more tolerable,
- less complex delivery system with subcutaneous administration and
- no preparation by the patient required.

Iloprost is a prostacyclin analogue marketed in both an intravenous and inhaled form. It is stable at room temperature and in ambient light and has a plasma half life of almost 30 minutes. The inhaled route promotes selective vasodilatation in the pulmonary circulation, optimization of ventilation-perfusion and minimization of systemic side effects. Disadvantages of the drug are increased cough and frequent administrations (six to nine times daily), with each administration lasting five to 10 minutes using a special nebulizer.

Beraprost is an orally active prostacyclin analogue that has been used to treat PAH in Japan since 1995. Galie, *et al*[6] showed its short-term efficacy in improving exercise capacity and symptoms. A similar, but longer study by Barst, *et al*[7] confirmed the short-term benefits of beraprost; however, these improvements were no longer evident at nine or 12 months. It is currently only approved for use in Japan.

Endothelin receptor antagonists

Endothelin-1 produced by endothelial cells contributes to vasoconstriction and proliferation of smooth muscle cells by acting on two receptor subtypes. Endothelin receptor A (ETA) is located on vascular smooth muscle cells and endothelin receptor B (ETB) is located on both vascular smooth muscle cells and vascular endothelium. Activation of these receptors on vascular smooth muscle cells leads to potent vasoconstriction and smooth muscle proliferation. Interestingly, activation of ETB on vascular endothelial cells causes increased nitric oxide and prostacyclin production and enhances clearance of ET-1, making the overall net effect of ETB activation unclear.

Bosentan is a nonselective endothelin receptor antagonist with proven efficacy for the treatment of PAH, showing improvement in:

- six-minute walk test,
- Borg dyspnea score,
- WHO functional class and
- time to clinical worsening.[8]

Side-effects include:

- headache,
- decreased hemoglobin,
- increased liver enzymes,
- flushing,
- edema and
- hypotension.

Bosentan is contraindicated in pregnancy and with concurrent use of cyclosporine or glyburide due to the increased risk of liver enzyme abnormalities. Bosentan is approved for patients with PAH in WHO functional class III.

Theoretically, selective antagonism of the ETA receptor would allow blocking of the deleterious vasoconstrictive and vascular smooth muscle proliferation mediated through ETA, while maintaining the vasodilator and ET-1 clearance actions of ETB. Sitaxsentan is a selective ETA receptor antagonist awaiting

FDA approval. This drug has an increased incidence of liver enzyme abnormalities similar to bosentan. It also causes a significant increase in INR requiring adjustment in warfarin dose. A second selective ETA receptor antagonist currently in phase III trials is ambrisentan, which may have a lower incidence of liver enzyme abnormalities.

Treatment with epoprostenol has been associated with improved survival rates, 85%, 63% and 55% at one, three and five years as compared to patients without treatment (58%, 33%, 28% respectively).

PDE-5 inhibitors

The third target pathway in PAH is the nitric oxide pathway. Decreased production of endogenous nitric oxide contributes to vasoconstriction and pulmonary arterial smooth muscle proliferation. Exogenous nitric oxide enhances production of cyclic guanosine monophosphate (cGMP) in the same fashion as endogenous nitric oxide (NO), leading to vasodilatation. Phosphodiesterase-5 (PDE-5) inhibitors selectively inhibit the enzyme responsible for the degradation of cGMP, resulting in more cGMP and thus, more vasodilatation.

Sildenafil, a PDE-5 inhibitor, dosed 20 mg t.i.d. is approved for treatment of PAH in the US without functional class restriction. Significant improvements in six-minute walk test, WHO functional class and pulmonary hemodynamics are demonstrated, with an improvement in the six-minute walk test persisting at one year of treatment. However, the incidence of clinical worsening does not differ between treated patients and placebo. Sildenafil is well tolerated and major side-effects include:

- headache,
- dyspepsia,
- sinus congestion,
- epistaxis and
- back pain.

No specific laboratory monitoring is required during treatment. Sildenafil is contraindicated in patients taking nitrate medications because of hypotension potentiation. A second PDE-5 inhibitor, tadalafil, is currently in Phase III trials.

Patients who do not respond to single-agent treatment with endothelin receptor antagonists (ERAs), PDE-5 inhibitors, or prostanoids, are considered for alternative treatments including combination therapy, lung transplantation, or atrial septostomy. In spite of the lack of published data on combination therapy, it is estimated that approximately 40% of patients are already on such therapy. Trials of combination therapy are currently underway.

Lung transplantation is considered for patients in WHO classes III and IV, although the outcome from lung transplantation is poorer than with other primary pulmonary diseases. Single lung, double lung and heart-lung transplants have all been performed successfully. Atrial septostomy is performed as a palliative measure.

Prognosis

Prognosis of PAH is dependent on several variables, including:

- underlying cause,
- response to vasodilators,
- WHO functional status,
- severity of hemodynamic derangement and
- performance on six-minute walk test.

PAH, secondary to CHD, has the best survival

rate, approximately 90% at five years, whereas PAH, secondary to HIV, has the worst survival rate, approximately 20% at three years time. (Figure 2). Response to CCBs in IPAH confers a better survival, with 94% of patients who responded to CCBs alive at five years time compared to 55% of nonresponders.[10] Several hemodynamic parameters studied have shown prognostic significance.[11] Survival worsens with higher WHO Functional Class, with median survival 58.6 months in Class I and II, 31.5 months in Class III and six months in Class IV.[12] Finally, performance on the six-minute walk test is predictive of prognosis.[13]

Have current therapies made a difference in survival rates associated with PAH?

Treatment with epoprostenol has been associated with improved survival rates, 85%, 63% and 55% at one year, three years and five years time as compared to patients without treatment (58%, 33%, 28% respectively).[14] Treprostinil and iloprost have shown improvement in six-minute walk distance and cardiac hemodynamics. No survival advantage has been elucidated. Bosentan has shown improved survival advantage of 85% at 12 months and 70% at 24 months when compared to predicted outcomes from the National Institute of Health Registry of 69% and 57%, respectively.[15] Sildenafil has demonstrated improvements in six-minute walk distance and cardiac hemodynamics, long-term survival data is not available.[16] Combination therapy is becoming more common practice in the management of PAH. Studies of various combinations are also underway. Overall, the recent advances in understanding of the disease processes of PAH and subsequently the development of targeted therapies have made a difference in outcomes, both with regards to quality of life and overall survival.

References
1. Simonneau G, Galie N, Rubin LJ, et al: Clinical classification of pulmonary hypertension. J Am Coll Cardiol 2004; 43(12SuppS):5S-12S.
2. Humbert M, Sitbon O, Chaouat A, et al: Pulmonary arterial hypertension in France: Results from a national registry. Am J Respir Crit Care Med 2006; 173(9):1023-30.
3. Badesch DB, Abman SH, Ahearn GS, et al: Medical therapy for pulmonary arterial hypertension. ACCP Evidence-based clinical practice guidelines. Chest 2004; 126(1Suppl):35S-62S.
4. Johnson SR, Mehta S, Granton JT: Anticoagulation in pulmonary arterial hypertension: A qualitative systematic review. Eur Respir J 2006; 28(5):999-1004.
5. Simonneau G, Barst RJ, Galie N, et al: Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension. A double-blind, randomized, placebo-controlled trial. Am J Respir Crit Care Med 2002; 165(6):800-4.
6. Galie N, Humbert M, Vachiery JL, et al: Effects of beraprost sodium, an oral prostacyclin analogue, in patients with pulmonary arterial hypertension: A randomized double-blind, placebo-controlled trial. J Am Coll Cardiol 2002; 39(9):1496-502.
7. Barst RJ, McGoon M, McLaughlin V, et al: Beraprost therapy for pulmonary arterial hypertension. J Am Coll Cardiol 2003; 41(12):2119-25.
8. Channick RN, Simonneau G, Sitbon O, et al: Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: A randomized, placebo-controlled study. Lancet 2001; 358(9288):1119-23.
9. McLaughlin VV, Presberg KW, Doyle RL, et al: Prognosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest 2004; 126(1Suppl):78s-92s.
10. Rich S, Kaufmann E, Levy PS: The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. NEJM 1992; 327(2):76-81.
11. Wensel R, Opitz CF, Anker SD, et al: Assessment of survival in patients with primary pulmonary hypertension: Importance of cardiopulmonary exercise testing. Circulation 2002; 106(3):319-24.
12. D'Alonzo GE, Barst RJ, Ayres SM, et al: Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann Intern Med 1991; 115(5):343-9.
13. Provencher S, Sitbon O, Humbert M, et al: Long-term outcome with first-line bosentan therapy in idiopathic pulmonary arterial hypertension. Eur Heart J 2006; 27(5):589-95.
14. Sitbon O, Humbert M, Nunes H, et al: Long-term intravenous epoprostenol infusion in primary pulmonary hypertension. Prognostic factors and survival. J Am Coll Cardiol 2002: 40(4):780-8.
15. McLaughlin VV, Sitbon O, Badesch DB, et al: Survival with first-line bosentan in patients with primary pulmonary hypertension. Eur Respir J 2005; 25(2):244-9.
16. Galie N, Ghofrani HA, Torbicki A, et al: Sildenafil use in pulmonary arterial hypertension (SUPER) Study Group. Sildenafil citrate therapy for pulmonary arterial hypertension. NEJM 2005; 353(20):2148-57.