Exercise-Induced Pulmonary Artery Hypertension in a Patient with Compensated Cardiac Disease:

Hemodynamic and Functional Response to Sildenafil Therapy

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We describe the case of a 54-year-old man who presented with exertional dyspnea and fatigue that had worsened over the preceding 2 years, despite a normally functioning bioprosthesis aortic valve and stable, mild left ventricular dysfunction (left ventricular ejection fraction, 0.45). His symptoms could not be explained by physical examination, an extensive biochemical profile, or multiple cardiac and pulmonary investigations.

However, abnormal cardiopulmonary exercise test results and a right heart catheterization—combined with the use of a symptom-limited, bedside bicycle ergometer—revealed that the patient's exercise-induced pulmonary artery hypertension was out of proportion to his compensated left heart disease. A trial of sildenafil therapy resulted in objective improvements in hemodynamic values and functional class. (Tex Heart Inst J 2015;42(1):50-4)

Key words: Exercise hemodynamics; exercise-induced pulmonary hypertension; exercise test; exercise tolerance; hypertension, pulmonary/diagnosis/drug therapy/etiology; phosphodiesterase 5 inhibitors/therapeutic use; pulmonary arterial hypertension; pulmonary vascular resistance; sildenafil

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Pulmonary artery hypertension (PAH) causes decreased exercise tolerance and carries a poor prognosis if untreated.^{1,2} According to the World Health Organization (WHO), suspicion of PAH necessitates diagnosis and categorization by means of comprehensive clinical and laboratory evaluation—including right heart catheterization (RHC)—to exclude such conditions as cardiac, pulmonary, sleep, thyroid, and connective-tissue disease, and then to guide appropriate treatment.³⁻⁶ Some patients exhibit normal hemodynamic profiles during standard RHC performed at rest, yet experience exercise-induced PAH. Although there is no standard definition or diagnostic protocol to enable the detection of exercise-induced PAH, the term “standard” RHC invariably implies the performance of RHC at resting baseline, followed by hemodynamic measurements at peak exercise. These procedures are performed either in conjunction with or independent of noninvasive cardiopulmonary exercise testing. Not only do we lack standard diagnostic criteria for exercise-induced PAH, we lack guidelines for its optimal medical management. Because this condition is thought to occur rarely, it has only recently been recognized as a distinct clinical entity.⁷⁻⁹

Case Report

We describe the case of a 54-year-old man who presented with exertional dyspnea and fatigue that had worsened over the preceding 2 years. He had a history of chronic—but mild and stable—compensated left ventricular (LV) dysfunction, with an ejection fraction of 0.45; 8 years earlier, he had received an aortic valve bioprosthesis. His medications included aspirin, atorvastatin, carvedilol, and lisinopril.

His symptoms could not be explained by physical examination, an extensive biochemical profile, or multiple cardiac and pulmonary investigations. These tests included a comprehensive laboratory panel, including thyroid function and connective-tissue disease screening, transthoracic and transesophageal echocardiography, a nuclear myocardial perfusion scan, cardiac magnetic resonance imaging (with and without gadolinium contrast), high-resolution computed tomography of the chest, computed tomographic angiography, pulmonary function studies with normal spirometry and diffusion capacity, and a sleep study that did not show evidence of central or obstructive

TABLE I. Results of Exercise Hemodynamic Study Supporting the Diagnosis of Exercise-Induced Pulmonary Artery Hypertension and Response to Sildenafil Therapy

Variable	Baseline		On Sildenafil (1 yr)	
	Resting	Peak Exercise	Resting	Peak Exercise
Mean arterial pressure (mmHg)	98	127	90	105
Pulmonary artery systolic pressure (mmHg)	22	70	24	40
Pulmonary artery diastolic pressure (mmHg)	6	20	10	11
Mean pulmonary artery pressure (mmHg)	13	46	14	20
Pulmonary capillary wedge pressure (mmHg)	6	9	9.5	11
Transpulmonary gradient (mmHg)	7	37	4.5	9
Pulmonary artery oxygen saturation (%)	71	31	79	60
Oxygen consumption (mL/min)	238	1,120	285	1,466
Cardiac output (L/min)	4.5	8.6	5.8	14.2
Pulmonary vascular resistance (Wood units)	1.5	4.5	0.8	1.2

TABLE II. Therapeutic Response to Sildenafil Therapy

Variable	Baseline	On Sildenafil (1 yr)
CPET data		
Exercise time (s)	300	640
Vo ₂ max (mL/kg/min)	13.4	18.5
Ve/Vco ₂ slope	41.5	33.1
Respiratory quotient	1.23	1.14
Echocardiographic data		
LVEDD (mm)	54	54
LVESD (mm)	38	38
Fractional shortening (%)	29	29
LVEF	0.45	0.45
Left ventricular mass (g)	222	235
Left atrial size (mm)	34	34
E/Ea	12	12
Mean AVG (mmHg)	6	5

AVG = aortic valve gradient; CPET = cardiopulmonary exercise test; E/Ea = ratio of E-wave (early filling from mitral inflow) to Ea (from tissue Doppler of mitral annulus); LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; Ve/Vco₂ slope = minute ventilation/carbon dioxide production relationship; Vo₂max = maximal oxygen consumption during CPET

tive sleep apnea. A routine RHC (at rest) yielded normal hemodynamic data, and a coronary angiogram revealed some luminal irregularities, but no evidence of obstructive coronary lesions.

The patient was referred to a cardiac rehabilitation program; however, he could not tolerate even low-level

exercise, raising concerns of deconditioning, anxiety, or even laziness. To investigate his symptoms further, we ordered a cardiopulmonary exercise test, which revealed impaired cardiac reserve, despite good effort. When RHC was repeated—this time in combination with a symptom-limited, bedside bicycle ergometer—testing revealed that the patient's exercise-induced pulmonary artery hypertension was out of proportion to his compensated left heart disease. His pulmonary artery capillary wedge pressure (PCWP) did not change substantially with exercise, but his mean pulmonary artery pressure (MPAP) increased more than 3-fold (from 13 to 46 mmHg). Moreover, there were considerable associated increases in transpulmonary gradient and pulmonary vascular resistance at peak exercise (Table I).

Empirical treatment with sildenafil (20 mg, 3×d) and the patient's resumption of a cardiac rehabilitation program produced objective hemodynamic and functional improvement by at least one New York Heart Association (NYHA) functional class (III to II). After a full year of sildenafil therapy, both the exercise RHC and the cardiopulmonary exercise testing (Table II) were repeated—apparently at the prompting of the patient's insurance carrier, as a condition for the continuation of sildenafil therapy as an off-label clinical indication.

These objective improvements in the patient's exercise hemodynamic values (Fig. 1) and functional capacity (Fig. 2) appeared to corroborate the worth of sildenafil therapy. In consideration of the reported salutary effects of sildenafil in patients with systolic or diastolic dysfunction and disproportionate PAH,¹⁰⁻¹² we repeated echocardiography at the same time. However, this failed to show any effect of sildenafil on the patient's LV systolic or diastolic function or on the functioning of his aortic valve prosthesis. Because there had been no other significant change in our patient's cardiac medical regi-

Fig. 1 Comparison of pulmonary hemodynamic function at baseline and at 1 year of sildenafil therapy shows marked decreases at peak exercise in **A**) mean pulmonary artery pressure, **B**) transpulmonary gradient, and **C**) pulmonary vascular resistance.

Fig. 2 Comparison of maximal exercise function at baseline and at 1 year of sildenafil therapy shows improvement, evidenced by **A**) increased peak maximal oxygen consumption ($\text{Vo}_2 \text{ max}$), **B**) improved ventilatory efficiency (indicated by a decrease in the Ve/Vco_2 slope, the minute ventilation/carbon dioxide production relationship), and **C**) increased treadmill exercise time.

men, we concluded that his observed clinical improvement could be attributed to the pulmonary vasodilatory effect of sildenafil.

Discussion

Although exercise-induced PAH has been described before⁷⁻⁹ and is considered to be an intermediate stage between normalcy and typical PAH,^{7,8} most reports involve

patients with WHO-I PAH, often with a background of connective-tissue disease¹³⁻¹⁵ (scleroderma, lupus, etc.). Our patient had a WHO-II background, symptoms disproportionate to his mild, stable LV dysfunction, and a recent record of multiple cardiac, pulmonary, and other tests, including several “normal” resting RHCs—before the diagnosis of exercise-induced PAH was ever made. A clue to his need for further evaluation was his poor cardiac performance during cardiopulmonary exercise

testing,^{16,17} despite his exceeding the anaerobic threshold (respiratory quotient >1)—which argued against simple deconditioning.

The confirmatory procedure consisted of RHC followed by supine bicycle ergometer testing in the catheterization laboratory.^{18,19} The patient's "normal" resting mean pulmonary artery pressure tripled, yet his PCWP remained normal, with a marked rise in his transpulmonary gradient and pulmonary vascular resistance, unaccompanied by a matched increase in cardiac output at peak exercise. Although his cardiac output increased almost 2-fold, we should note that normal individuals increase their cardiac output 3- to 5-fold at maximal exercise.¹⁹

A crucial determinant of the accuracy of exercise RHC data includes the ability to directly measure oxygen consumption separately, at rest and at peak exercise. This requires special instrumentation and can be laborious. However, assumptions that have their basis in resting-data-derived calculations lead to major interpretation errors. In our laboratory, we have found such good correlation between direct measurements of exercise oxygen consumption and cardiopulmonary exercise testing-derived values that the latter can be used as a surrogate for the former.

After confirmation of a diagnosis of exercise-induced PAH, selection of appropriate therapy is equally problematic, particularly when the patient has a WHO-II background. Some medical literature supports sildenafil's use in exercise-induced PAH patients who have a background of other pulmonary diseases²⁰ (WHO-III), but not in patients with cardiac dysfunction (WHO-II). There is weak (and indeed conflicting) evidence about the potential benefits of sildenafil in treating systolic¹⁰⁻¹² or diastolic^{21,22} LV dysfunction; our patient had no change in echocardiographically derived cardiac values. It is also noteworthy that he had no significant increase in his left-sided filling pressures (PCWP) at rest or during peak exercise after a year of sildenafil therapy, which is a theoretical concern limiting the routine application of specific pulmonary vasodilatory therapy in WHO-II patients.

Our patient's rather atypical presentation illustrates that exercise-induced PAH can coexist as the only manifestation of disproportionate PAH in patients with otherwise stable left heart dysfunction, even when RHC at rest is normal.

Clinicians should suspect exercise-induced PAH when the following criteria are present: 1) excessive exertional dyspnea and fatigue, out of proportion to the degree of LV dysfunction and in the absence of resting symptoms (that is, NYHA class II–III, but not IV); 2) the exclusion of other cardiac, pulmonary, connective-tissue, systemic, or sleep disorders; 3) normal resting hemodynamic values (by RHC); and 4) abnormal cardiopulmonary exercise testing due to cardiac limitation

yet adequate effort (low maximal oxygen consumption [VO_2 max], high slope of ventilation to carbon dioxide production, and respiratory quotient >1). The best way to confirm the diagnosis involves exercise RHC with meticulous measurements of oxygen consumption at rest and during peak exercise.

Confirmatory findings include the following: 1) a marked increase of MPAP, transpulmonary gradient, and pulmonary vascular resistance at peak exercise with no accompanying significant change in PCWP (which remains normal); 2) a modest increase (less than 2-fold) or no significant change in cardiac output; and 3) a marked drop in pulmonary arterial oxygen saturation.

If the operator is unable to measure oxygen consumption in the catheterization laboratory, it is probably not unreasonable to use a derived value from a recent cardiopulmonary exercise test, with use of the formula,

$$\text{Peak exercise whole-body oxygen consumption} = (\text{VO}_2 \text{ max}) \times (\text{body weight in kg}).$$

Notwithstanding the obvious limitation of this paper as a single case report, we maintain that it provides diagnostic insights and that its description of the clinical course of our patient supports the therapeutic potential of sildenafil in exercise-induced PAH. We point out that the benefits of sildenafil are mediated not through changes in cardiac function, but through pulmonary vasodilatory mechanisms.

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