Section Editor
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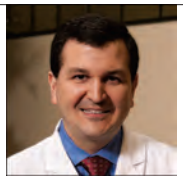

Section Editor
Fernando Torres, MD

The Clinical Trials Update highlights new and ongoing research trials that are evaluating therapies for pulmonary arterial hypertension. In this issue, Deborah Jo Levine, MD, describes a recent trial of sildenafil.

This issue of *Advances* focuses on the important and most challenging issue of the left heart and pulmonary hypertension (PH). We are all aware of the many patients who are referred to pulmonary arterial hypertension (PAH) clinics who have Group 2 PH with diastolic dysfunction and/or mixed disease rather than classic Group 1 PH (PAH). As with all patients being evaluated for PAH, these patients require a thorough evaluation, which includes right heart catheterization (and when appropriate, a left heart catheterization) prior to making therapeutic decisions. Patients with diastolic dysfunction carry a specific risk in being treated with pulmonary vasodilators, as this group of drugs can precipitate pulmonary edema or worsen heart failure. Optimization with heart failure regimens has been the standard treatment in most of these patients with Group 2 PH.

This issue's column focuses on a single-center, long-term study evaluating whether cardiac function (diastolic function) *may* be a target for chronic PDE-5 inhibition. In this small study, authors evaluated the use of chronic sildenafil in patients with stable heart failure. While PDE-5 inhibitors are not recommended at present for these patients, this study brings forth the possible utility of this class of therapy to target diastolic dysfunction.

Prior animal studies and small, short-term clinical studies have evaluated the use of PDE-5 inhibition as a potential adjunctive therapy in the management of stable heart failure patients. In their recent study, "PDE5 inhibition with sildenafil improves left ventricular diastolic function cardiac geometry, and clinical status in patients with stable systolic heart failure: results of a 1-year, prospective, randomized, placebo-controlled study," Guazzi et al address the effects of the use of chronic PDE-5 inhibitors (sildenafil) on diastolic function and clinical status by tissue Doppler imaging, cardiopulmonary exercise testing (CPET), and quality of life score.[1]

The primary endpoints of the study were the evaluation of drug-induced benefits of chronic sildenafil on left ventricular (LV) diastolic function, chamber dimensions, and mass. Secondary endpoints included functional capacity and quality of life.

This was a double-blind, randomized, placebo-controlled trial. After an initial assessment and admission into the study, 45 male patients who were clinically stable with heart failure (cardiomyopathy) (NYHA Class II-III) were given either placebo or sildenafil 50 mg po tid, in addition to their baseline therapy. The trial duration was 1 year. In all participants, symptoms, physical examination, ECG, and blood pressure measurements were performed monthly. Doppler echocardiography, NT-proBNP measurements, CPET, and quality of life measurements were assessed at 6 and 12 months in both groups. Quality of life assessment was done on all patients using a scale designed for patients with heart failure.

At the initiation of the study, left ventricular ejection fraction (LVEF), pulmonary artery systolic pressure (PASP), Doppler derived diastolic data, and CPET variables were evaluated for baseline measures. After these studies were completed, patients were given 50 mg po of sildenafil, and 2 hours later these same variables were reevaluated to assess the acute response to sildenafil.

There were no statistically significant differences between the baseline characteristics of participants in the placebo vs treated groups. Both groups responded similarly to the acute trial of 50 mg sildenafil. There was a decrease in PASP and improvement in exercise and ventilatory status, but LVEF and diastolic function did not change.

Over 1 year, the left atrial volume index and LV mass index were unchanged in the placebo group but significantly decreased in the sildenafil group, suggesting reversal of remodeling. In the sildenafil group, there was a significant increase in LVEF (29.5% to 34.9% and 36.3% at 6 and 12 months respectively, $P=0.01$). These were significantly different then those in the placebo group, which did not show this change. Diastolic measures of LV function showed sustained improvement at both 6 months and 1 year in the sildenafil group only. Plasma NT pro-BNP levels increased in the placebo group over 12 months, but fell by a mean of 320 pg/ml with sildenafil ($P=0.01$). PASP significantly decreased at both 6 and 12 months in the sildenafil group only (PASP decreased from 37.1 mm Hg to 24.2 mm Hg at 6 months and to 24.0 mm Hg at 12 months, $P=0.01$). CPET at 6 and 12 months showed a significant improvement over baseline peak VO2 and VO2 anaerobic threshold and a decrease in Ve/VCO2 slope in the sildenafil group. The quality of life assessment documented a significant and sustained improvement in breathlessness, fatigue, and emotional function in the sildenafil group only.

During the trial, there were 3 hospitalizations in the placebo group and 1 in the sildenafil group (all for new onset atrial fibrillation). Adverse reactions in the

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sildenafil group consisted of flushing in 3 patients and headache in 2 patients.

The authors concluded that in this group of stable heart failure patients, long-term use of sildenafil was well tolerated. The results point to some improvement in the LV and diastolic function properties and cardiac geometry. The authors found that these patients improved their functional capacity and clinical status as well.

The benefits of PDE-5 inhibition have been demonstrated in patients with Group 1 PAH in multiple trials. However, the question of whether this class of drugs or other PAH-specific therapies may play a role in those patients who come to our clinics with PH associated with left heart disease needs to be evaluated in larger clinical trials. Currently, the use of these agents remains limited to those who have documented PAH by right heart catheterization. This study, along with others, explores the use of PDE-5 inhibitors in patients with Group 2 PH and may provide rationale for the development of future trials to evaluate patients with Group 2 PH.

Reference

1. Guazzi M, Vicenzi M, Arena R, Guazzi MD. PDE5 inhibition with sildenafil improves left ventricular diastolic function, cardiac geometry, and clinical status in patients with stable systolic heart failure: results of a 1-year prospective, randomized, placebo-controlled study. *Circ Heart Fail.* 2011; 4(1):8-17.

Guest Editor's Memo

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the least important of all the findings that echocardiogram provides.

Right heart catheterization remains the ultimate arbiter and, like any tool, it is critical for the operator to know how to maneuver and interpret the information correctly. Dr Mathier provides the key do's and don'ts of performing right heart catheterization and how to avoid the pitfalls in interpreting the data. Furthermore, he explores the often asked question "What is PH 'out of proportion'?" Finally, Dr Champion walks us through the therapeutic realm for PH associated with left heart disease, most notably those therapies that have been studied and found to be ineffective. The promising aspects of phosphodiesterase-5 inhibitors are discussed with the need for randomized clinical trials to determine its potential usefulness in this population. The Roundtable discussion engages Drs Alvarez, De Marco, Robbins, and Semigran, who share their views on how HFpEF impacts their clinical practice and how they approach this entity.

Though we may not have a clear picture yet, we are making strides in improving our understanding and coming to appreciate PH associated with diastolic dysfunction. I believe this issue will prove to be a useful resource in managing this increasing group of PH patients.

Finally, I would like to thank Erika Berman Rosenzweig for her encouragement and guidance in completing this issue.

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