Journal of the American College of Cardiology Vol. 50, No. 22, 2007

Published by Elsevier Inc.
ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2007.07.075

EDITORIAL COMMENT

Type 5 Phosphodiesterase Inhibition in Heart Failure

The Next Step*

Steven R. Goldsmith, MD, FACC

Minneapolis, Minnesota

Those who cannot remember the past are condemned to repeat it.
—George Santayana (1)

The possibility that selective inhibition of type 5 phosphodiesterase (PDE_5) might be helpful in heart failure (HF) is currently receiving attention. This approach consistently and significantly reduces pulmonary vascular resistance (PVR) by inhibiting the hydrolysis of cyclic guanosine monophosphate in the pulmonary vasculature (2). As a result, right ventricular (RV) function and exercise capacity improve in patients with pulmonary hypertension (3,4). Based on the efficacy and safety of these compounds in that setting, several investigators have begun to study this class of therapy in patients with HF caused by left ventricular (LV) systolic heart failure (SHF). The creative and well-conducted study by Guazzi et al. (5) in this issue of the *Journal* represents the latest of these investigations. The purpose of this Editorial Comment is to review this study, place it in the context of current knowledge, and suggest a possible next step in the investigation of the therapeutic potential of these interesting compounds for SHF.

See page 2136

Guazzi et al. (5) studied the effects of sildenafil in patients with chronic stable SHF on contemporary neurohormonal inhibitory therapy and diuretics. They set out 3 goals for their study: 1) to show that acute effects of sildenafil on a number of physiological parameters could be safely maintained with up to 6 months of treatment; 2) to investigate the possibility that a novel mechanism, namely improving the sensitivity of the ergo-ventilatory reflex, might contribute to any benefits seen; and 3) to establish a rational basis for further study of this compound in heart failure. How well did they succeed?

In my opinion, the first goal was clearly met. Compared with placebo, 6 months of administration of sildenafil (50 mg twice daily) reduced pulmonary artery pressure (estimated from echocardiographic Doppler study), improved ventilatory efficiency and peak oxygen consumption, improved flow-mediated vasodilation in the brachial artery, and improved the sensitivity of the ergo-ventilatory reflex (a reflex that couples mechanoreceptors and/or chemoreceptors in exercising skeletal muscle to the control of ventilation) (6,7). Findings present in acute experiments were reproduced at 3 and 6 months in the active treatment group. In addition, one component of an unspecified quality-of-life questionnaire, breathlessness, was improved with active treatment. There were no untoward effects of therapy.

These findings are impressive. The acute experiments confirm results from other acute studies in SHF (8,9). An important feature of the current study design was the assessment of the response of all variables (other than those assessed on the heart failure questionnaire) to active therapy in all subjects before randomization to minimize the chance that differences in response between groups could have been caused by intrinsic differences in responsiveness. In fact, both groups responded identically to acute therapy, whereas only the sildenafil-treated group showed similar responses at 3 and 6 months. Interestingly, there was little difference in the magnitude of the response of any variable between acute administration and 3 months of therapy with sildenafil, and only trends toward any additional improvement at 6 months. The implication of the time course of these responses is clearly that whatever the mechanism responsible for the improvements, the effect is likely to be pharmacological rather than biological because the results of major changes in gene expression or structure would presumably take longer to become evident.

Sildenafil therefore may be an effective agent in patients with chronic SHF by reducing pulmonary artery pressure and by improving ventilatory efficiency and exercise capacity and the associated symptom of breathlessness. The next issue is the nature of the mechanism producing these effects and the implications of this mechanism or mechanisms for further investigation. This leads to the examination of how well the investigators succeeded in meeting their second goal, namely investigating the possibility that improvements in ergo-ventilatory reflex function contribute significantly to the hemodynamic and ventilatory effects seen. In my opinion, although the study shows a clear effect of sildenafil on this reflex, any speculation about cause and effect is premature. This is an interesting reflex that has been shown to be abnormal in patients with HF (6,7), but little is known about factors influencing its function. It is tempting to assume that improved nitric oxide donation (presumptively the mechanism of the improved flow-mediated vasodilation shown in the forearm circulation) also improved the function of this reflex. Proof would require future experiments with an inhibitor of nitric oxide generation or effect. But

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the Cardiology Division, Hennepin County Medical Center, and the University of Minnesota, Minneapolis, Minnesota.

JACC Vol. 50, No. 22, 2007
November 27, 2007:2145–7

whatever the mechanism by which the reflex function improved, it is entirely plausible that the improvement occurred in parallel with the other responses shown. Nothing in the data allows any conclusion about causality in either direction (i.e., from the reflex to the ventilatory and hemodynamic responses, or vice versa). Therefore, although these data are novel and intriguing, the most that can really be said is that improvements in this reflex represent another possible mechanism by which this class of agents might improve exercise capacity and ventilatory function in patients with SHF. Simply improving pulmonary perfusion as a result of lowered pulmonary vascular resistance could have had a major effect on physiological dead space and possibly on other receptors and reflexes originating within the pulmonary circulation. These effects could also have led to improvements in ventilatory efficiency, exercise capacity, and the sensation of breathlessness.

What then should we do in view of this study, which nicely extends acute experiments by their own group and those of others working in this field (8,9)? This question relates to their third goal, that of providing a rational basis for further study. Here, in my opinion, although providing important data that may be useful in future studies, they have not made a compelling case showing that such study is yet warranted. My concern follows from important mechanistic questions that are not yet resolved, and that I think need to be resolved if we are not to find ourselves ruefully pondering Santayana several years hence. Should we proceed without more and crucial information about how these drugs work in SHF?

The most consistent effect of these drugs is to lower PVR. Little if any effect is seen on systemic vascular tone (although the observation on improved flow-mediated vasodilation certainly suggests activity in the peripheral circulation). Cardiac output, however, frequently increases, both in patients with primary pulmonary hypertension and in those with SHF (4,8–10). Furthermore, in patients with predominantly RV dysfunction, cardiac output increases with sildenafil but not the inhalation of nitric oxide at comparable reductions in the pulmonary vascular resistance (10). These observations, of course, strongly suggest an inotropic effect of inhibiting PDE_5. Yet it has been difficult to demonstrate PDE_5 in human myocardium (11), and cardiac output does not increase when PDE_5 is inhibited in normal humans or those with coronary disease (12,13). Other experiments in normal myocardium have shown that PDE_5 inhibition actually blunts the inotropic response to adrenergic agonists (14). At a minimum, one would have to conclude that the actions of PDE_5 and its inhibition in normal myocardium are unclear, and may depend on whether effects are assessed under basal conditions or with adrenergic stimulation.

A recent and important investigation by Nagendran et al. (15), however, extends our knowledge of this physiology by studying PDE_5 effects in abnormal human myocardium. These investigators confirmed that although PDE_5 was not found in normal human RV myocardium, it was found in diseased, hypertrophied RV myocardium, and it was possible to show an inotropic effect of PDE_5 inhibition in this tissue. The proposed mechanism is indirect inhibition of PDE_3 as a result of increased guanosine monophosphate signaling, with subsequent cyclic adenosine monophosphate-mediated effects as would be expected. In the accompanying editorial, Kass (16) notes that although these findings conflict to some extent with other reported data and will require confirmation, the data are intriguing and may help to reconcile the apparent paradox of an inotropic effect of PDE_5 inhibition in patients with RV dysfunction, but not in normal subjects. Nagendran et al. (15) laud this finding as yet another reason that this type of therapy might be effective in primary pulmonary hypertension with abnormal RV function. However, if the same type of response were to be demonstrable in diseased, hypertrophied left ventricular tissue (and as Kass [16] notes, this seems more likely than not), there would be significant cause for concern about the safety of long-term administration of these agents in patients with SHF. We have learned, painfully and repeatedly, that inotropic intervention in HF, including that based on PDE_3 inhibition, is dangerous (17).

In view of these considerations, I believe the next step in the development of PDE_5 inhibitory therapy for SHF should be to repeat the experiments of Nagendran et al. (15) in human LV myocardial tissue. If the results are negative, in view of the promising signals from the small clinical series reported to date, a larger outcomes trial would be reasonable. However, if PDE_5 is found in LV tissue, and if an inotropic effect is shown as a result of its inhibition, then a very hard look would have to be taken at the possible clinical relevance of such findings. A possible increase in mortality caused by chronic inotropic stimulation would have to be set against the likelihood of symptomatic improvement from the effects of PDE_5 inhibition in the lung. It is true, of course, that the use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone antagonists, adrenergic antagonists, and defibrillators might diminish the risks of chronic low-dose PDE3 inhibition in SHF. But we do not know that, whereas we do have the tools and techniques at our disposal to learn whether such concerns should enter into consideration of future development of these compounds. In other words, we have the ability not only to remember our past history with other agents that inhibit phosphodiesterase in chronic SHF, but also to avoid repeating previous mistakes. I believe we should make every attempt to do so before embarking on larger trials in SHF with these interesting and potentially useful compounds.

Reprint requests and correspondence: Dr. Steven R. Goldsmith, Professor of Medicine, University of Minnesota, Division of Cardiology, Hennepin County Medical Center, 701 Park Avenue, Minneapolis, Minnesota 55415. E-mail: srg_hcmc@yahoo.com.

REFERENCES

1. Santayana G. The Life of Reason. Available at: http://en.wikiquote.org/wiki/George_Santayana. Accessed October 23, 2007.
2. Rabe KF, Tenor H, Dent G, Schudt C, Nakashima M, Magnussen H. Identification of PDE isozymes in human pulmonary artery and effect of selective PDE inhibitors. Am J Physiol 1994;266:L536–43.
3. Galie N, Ghofrani HA, Torbicki A, et al., Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study Group. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med 2005;353:2148–57.
4. Michelakis ED, Tymchak W, Noga M, et al. Long-term treatment with oral sildenafil is safe and improves functional capacity and hemodynamics in patients with pulmonary arterial hypertension. Circulation 2003;108:2066–9.
5. Guazzi M, Samaja M, Arena R, Vicenzi M, Guazzi MD. Long-term use of sildenafil in the therapeutic management of heart failure. J Am Coll Cardiol 2007;50:2136–44.
6. Ponikowski PP, Chua TP, Francis DP, Capucci A, Coats AJ, Piepoli MF. Muscle ergoreceptor overactivity reflects deterioration in clinical status and cardiorespiratory reflex control in chronic heart failure. Circulation 2001;104:2324–30.
7. Scott AC, Francis DP, Davies LC, Ponikowski P, Coats AJ, Piepoli MF. Contribution of skeletal muscle "ergoreceptors" in the human leg to respiratory control in chronic heart failure. J Physiol 2000;529:863–70.
8. Guazzi M, Tumminello G, Di Marco F, Fiorentini C, Guazzi MD. The effects of phosphodiesterase-5 inhibition with sildenafil on pulmonary hemodynamics and diffusion capacity, exercise ventilatory efficiency, and oxygen uptake kinetics in chronic heart failure J Am Coll Cardiol 2004;44:2339–48.
9. Lewis GD, Lachman J, Camuso J, et al. Sildenafil improves exercise hemodynamics and oxygen uptake in patients with systolic heart failure. Circulation 2007;115:59–66.
10. Michelakis E, Tymchak W, Lien D, Webster L, Hashimoto K, Archer S. Oral sildenafil is an effective and specific pulmonary vasodilator in patients with pulmonary arterial hypertension: comparison with inhaled nitric oxide. Circulation 2002;105:2398–403.
11. Cremers B, Scheler M, Maack C, et al. Effects of sildenafil (Viagra) on human myocardial contractility, in vitro arrhythmias, and tension of internal mammaria arteries and saphenous veins. J Cardiovasc Pharmacol 2003;41:734–43.
12. Jackson G, Benjamin N, Jackson N, Allen MJ. Effects of sildenafil citrate on human hemodynamics. Am J Cardiol 1999;83:13C–20C.
13. Herrmann HC, Chang G, Klugherz BD, Mahoney PD. Hemodynamic effects of sildenafil in men with severe coronary artery disease. N Engl J Med 2000;342:1622–6.
14. Borlaug BA, Melenovsky V, Marhin T, Fitzgerald P, Kass DA. Sildenafil inhibits beta-adrenergic-stimulated cardiac contractility in humans. Circulation 2005;112:2642–9.
15. Nagendran J, Archer SL, Soliman D, et al. Phosphodiesterase type 5 is highly expressed in the hypertrophied human right ventricle, and acute inhibition of phosphodiesterase type 5 improves contractility. Circulation 2007;116:238–48.
16. Kass D. Hypertrophied right hearts get two for the price of one**:** can inhibiting phosphodiesterase type 5 also inhibit phosphodiesterase type 3? Circulation 2007;116:233–5.
17. DiBianco R, Shabetai R, Kostuk W, Moran J, Schlant RC, Wright R. A comparison of oral milrinone, digoxin, and their combination in the treatment of patients with chronic heart failure. N Engl J Med 1989;320:677–83.