EDITORIAL

Sildenafil in Heart Failure: An Indication with Growing Evidence, but Still Inconclusive

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SILDENAFIL IN HEART FAILURE

Determinants of exercise capacity in patients with heart failure are numerous: diastolic left ventricular function, pulmonary pressure, right ventricular function, oxygen carrying capacity, pulmonary function, muscle mass, peripheral vasodilator capacity. The vascular tone is subject to the influence of different mediators, while the sympathetic nervous system, renin-angiotensin system, and endothelin cause vasoconstriction and endothelial dysfunction, nitric oxide, natriuretic peptides, and renal prostaglandins have the opposite effect. Nitric oxide, long known as an endothelium relaxation factor, has the cyclic GMP as a second messenger, which in turn is degraded by phosphodiesterase 5 in the pulmonary vasculature. Eleven families of phosphodiesterase inhibitors with different affinities for cyclic nucleotides cAMP and cGMP have been identified. Five is highly specific for cGMP. (1)

In recent years, there has been increasing information about a reflex phenomenon originated at the level of the skeletal muscle, as a result of the stimulation of ergoreceptors sensitive to the accumulation of degradation products and mechanical stimulation. The ergoreflex causes an increase in the sympathetic tone and in ventilation during exercise, with increased sensation of dyspnea. (2)

Vasodilators can improve many of the parameters mentioned; in hemodynamic terms, their use is associated with reduction in preload and afterload of both ventricles, and with decreased systemic and pulmonary resistance. Sildenafil is a phosphodiesterase 5 inhibitor. Its vasodilator action was first used to treat erectile dysfunction. It was then used in patients with pulmonary hypertension, and in recent years, in patients with heart failure. In this context, some studies have assessed the ability of this drug to improve parameters of cardiac and endothelial function, as well as exercise capacity. (3) The magnitude of the hemodynamic effects of sildenafil is similar to that of nitric oxide. (4)

The beneficial effects attributed to sildenafil include improvement in loading conditions with a decrease in pulmonary pressure, reduction of the ratio of pulmonary and systemic vascular resistance (implying a preferential vasodilator effect at the level of the pulmonary vascular bed), improvement of right ventricular function, and attenuation of endothelial dysfunction. Minute volume increases and aortic stiffness decreases. (5) All these result in improved muscular perfusion and increased levels of maximum oxygen consumption (VO2 max). The effects are observed as early as 60 minutes after intake. Acute effects of sildenafil also showed decreased ergoreflex influence on ventilation, and a decrease in VE / VCO2 slope, which expresses –among other things– increased pulmonary dead space, hypoperfusion of the lungs, and pulmonary interstitial space filled with fluid from the intravascular space due to increased pulmonary capillary pressure. (6) Replication of acute effects have been observed in the treatment at 1, (7) 3 and 6 months. (8, 9)

In all the series, the patients clearly benefited were those with secondary pulmonary hypertension. As we all know, pulmonary hypertension and right dysfunction impose worse prognosis on patients with left ventricular failure. (10) However, for different reasons, other vasodilators like bosentan and epoprostenol have not proved useful in patients with heart failure and secondary pulmonary hypertension. (11, 12)

THE VALUE OF THE 6-MINUTE WALK

The determination of VO2 max in cardiopulmonary test has been traditionally considered as the preferred exercise test in heart failure due to its reproducibility and prognostic value. (13) In comparison, the 6-minute walk emerges as a simpler and more economical alternative, with a strong inverse relationship with pulmonary pressure and a direct relationship with right ventricular function. (14) The distance walked in 6 minutes proved to be a strong predictor of mortality in the SOLVD study. (15) A systematic review of literature confirms its discriminative power and its relation to maximal O2 consumption, mainly when the distance walked is less than 490 meters. (16) In a severely involved population, it can be understood as a maximal exercise test, since O2 consumption is not different from that in a cardiopulmonary test. (17) While it may be argued that a 'learning effect' can be found in a second test performed shortly after the first one, it does not exceed 10% of the distance at baseline. (18)

Another systematic review of the results obtained in 47 randomized trials with studies showed a significant improvement in walking, mainly in those which included more severe patients. The increase of distance walked varied according to target population, age, severity of

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the condition, and agent used. Most studies on the cited drugs demonstrated no improvement in functional capacity, but 5 out of the 7 which showed symptomatic improvement also demonstrated improvement in walking. (19) One study has shown that a substantial adjustment of the usual treatment may improve significantly the exercise capacity, with an overall increase of 80 meters in the distance walked after 2 weeks of optimal treatment. (20) Concerning the effect of sildenafil on VO2 max and walking at 12 weeks, an increase of 1.8 ml/kg/min and 29 meters respectively has been reported. (21)

COMMENTS ON A STUDY

The study by Curotto Grasiosi et al (22) explores the ability of sildenafil –compared with placebo– to acutely improve exercise capacity. Its population is clearly sick: two thirds of the patients are in FC III (corroborated by the low walking distance at baseline, on average less than 240 meters in both arms) and the mean ejection fraction is 26.5%. Particularly noteworthy is the high rate of use of neurohormonal antagonists. As in other studies already mentioned, a dose of 50 mg of sildenafil is used. Unlike other studies that performed hemodynamic measurements or cardiopulmonary test, this study uses the 6-minute walk test to determine the functional capacity before and after intervention. Its outcomes are remarkable: an increase of the distance walked < 5% in the placebo arm, and > 40% in the sildenafil arm. The outcomes of this trial, performed in our country, confirm the evidence of previous trials. The amount of improvement in exercise capacity impresses and is higher than in other studies, perhaps because it includes more severe patients with greater chances of improvement.

We do miss some determinations that could have shed more light on the outcomes. The assessment of right ventricular function and pulmonary pressures would have allowed to complete the clinical characterization of patients and compare them with patients from other publications. Similarly, the same effect would have caused to determine the prevalence and severity of mitral regurgitation, which we assume significant because of the target population. Describing the changes in pulmonary circulation and in the amount of mitral regurgitation, together with changes in blood pressure as an expression of peripheral vasodilation, may help explain the significant improvement in functional capacity in general within treated patients, and even find reasons to distinguish responders from non-responders, or different response capacity. Perhaps, then, a continuation of this study, with more patients and further evaluation, will serve the authors to deepen the trace they have already drawn. Along the same lines, a determination of BNP or NT proBNP as expression of wall stress before and after intervention could work similarly.

It is clear that the evidence from this study and others already discussed is still not enough to consider sildenafil or similar drugs a clear indicator in the context of chronic heart failure. In the past, other interventions showed improvement in functional capacity but, at the same time, were a threat to vital prognosis. (23, 24) Will the effects of the intervention be sustained over time? Does it represent a long-term risk to inhibit cGMP degradation, as it does in the case of cAMP? In case it proves to be safe enough, will it be a universal or useful indicator in some subgroups? The door for further research is open to the authors of this and other studies on this topic.

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