To the Editor:

A subgroup of participants (n=48) in the RELAX trial underwent a comprehensive cardiovascular assessment after sildenafil treatment. After 24 weeks, sildenafil decreased arterial elastance while reducing LV peak power and stroke work. These effects were attributed to deleterious effects on LV contractility, despite salutary effects on vasculature. Before referring to the connotations salutary or deleterious, authors should be invited to reflect on some critical issues.

1. Patients were pooled regardless of clinical phenotype. Hypertensive, diabetic, ageing, female, and obese patients may share some common end point, but evolve along distinct pathophysiological processes. Pooling data from heterogeneous study patients confounds interpretation of averaged data and has all too often led to conclude that some promising drugs were ineffective.

2. Any perturbation of the cardiovascular system triggers compensatory mechanisms to reestablish homeostasis. Central to rebalancing homeostasis are subtle modulations in the crosstalk between LV and the vasculature to optimize LV pump performance on a beat-to-beat basis through alterations in the sequence of reflected waves and their effect on time of onset of relaxation. With arterial stiffening, reflected waves reach the LV early during ejection, resulting in prolongation of ejection duration. With decreased arterial impedance, reflected waves reach the LV only in late ejection. As the myocardium becomes sensitive to loading during the second half of ejection, premature relaxation ensues, often accompanied by some slowing of relaxation speed. As the transition from load-independent to load-dependent myocardium is established shortly before peak pressure, early onset of relaxation may result in some decrease in peak ventricular pump performance as part of a physiological unloading effect. This balanced gauging of ventricular-arterial shifts in loading sequence is an essential physiological feature of cardiovascular homeostasis and underlies the observations by Borlaug et al. A potentially confounding factor in the present subgroup is the LV hypertrophy in several patients, which already by itself and regardless of the pathogenesis (hypertensive, diabetic, ageing) delays the onset of relaxation. Only a detailed analysis of all time intervals can help to distinguish salutary, physiological from deleterious effects.

3. Because of their pleiotropic action on homeostasis, the novel generation of endothelium-mediated or -substituting drugs, like sildenafil, should be administered gently and at the lowest possible dosages to reestablish or maintain optimal homeostasis while avoiding any ventricular-arterial mismatch. In this study, the high dosage of sildenafil (180 mg/d) will persistently decrease impedance and push the finely tuned arterial-ventricular balance to a limit, resulting in unintended decrease in peak power or stroke work. High dosages will, moreover, further exaggerate shifts in loading from early to late predominance through direct effects on onset of relaxation. Accordingly, the drug is not deleterious. The dosage just may be too high.

As a final minor note, because peak power and stroke work indices are typical parameters of ventricular pump performance, the myocardial muscle term contractility should in my opinion best not be used here.

Disclosures

None.

Dirk L. Brutsaert, MD, PhD
Faculty of Medicine and Pharmacy
University of Antwerp
Antwerp, Belgium

Gilles W. De Keulenaer, MD, PhD
Laboratory of Physiopharmacology
University of Antwerp
Antwerp, Belgium

References


Letter by Brutsaert and De Keulenaer Regarding Article, "Effects of Sildenafil on Ventricular and Vascular Function in Heart Failure With Preserved Ejection Fraction"
Dirk L. Brutsaert and Gilles W. De Keulenaer

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