Type 5 Phosphodiesterase Inhibition
The Focus Shifts to the Heart

Marc J. Semigran, MD

Previous studies of the effects of increasing cardiomyocyte cGMP by NO stimulation of guanyl cyclase have identified a direct negative inotropic effect and a modulation of the effect of adrenergic stimulation on contractile function. This effect is thought to be clinically important in mediating the depression in contractility observed in sepsis, transplant rejection, myocarditis, and trauma. The natriuretic peptides and NO share cGMP as a common intracellular signaling molecule, and natriuretic peptides have also been observed to decrease contractility of isolated ventricular myocytes. The clinical importance of this finding is uncertain, because both atrial natriuretic peptide and B-type natriuretic peptide increase cardiac output while reducing ventricular preload and afterload in heart failure patients and, as has been shown with atrial natriuretic peptide, without altering myocardial contractility or diastolic function.

cGMP generated by stimulation of either membrane-bound or soluble guanyl cyclase would be expected to be metabolized by PDE. Eleven families of cyclic nucleotide PDEs have been described, of which several, including type 5 (PDE5), utilize cGMP as substrate. Immunohistochemistry studies did not initially identify PDE5 in cardiomyocytes, and both functional and immunochemical assays appeared to characterize cGMP hydrolysis activity in human vascular tissue as being due to PDE1 activity. More recent studies have identified PDE5 in both murine and canine cardiomyocytes, with PDE5 mRNA expression identified in human heart. Although the latter finding was initially thought to be related to contamination by vascular smooth muscle tissue, the present study by Borlaug et al supports the presence of PDE5 activity in human cardiomyocytes.

The vascular effects of PDE5, including its pulmonary vascular effects, have been well recognized since its initial identification and appreciation as a pharmacological target, and PDE5 inhibition in corpus cavernosal vascular smooth muscle has been a major breakthrough in the treatment of erectile dysfunction. Inhibition of PDE5 also leads to pulmonary vasodilation that is additive to the effect of inhaled NO and has led to their combined use in neonates with pulmonary hypertension and to approval by the US Food and Drug Administration of sildenafil alone for the treatment of adult pulmonary arterial hypertension. Unfortunately, the efficacy of PDE5 inhibitors as coronary vasodilators appears to be less clinically useful, because PDE5 inhibition improves coronary flow reserve in both diseased and nonstenotic coronary arteries similarly.

Now, a picture of the role of PDE5 in cardiomyocyte function is beginning to emerge from both preclinical studies and the work of Borlaug et al. Using immunohistochemistry, Sznazki et al observed PDE5 to be present in cardiomyo-
cytes in normal dogs and in a tachycardia-induced model of cardiac dysfunction; however, the development of heart failure was accompanied by a reduction in PDE5 activity and its translocation away from the ε bands of the sarcomere. PDE5 appeared to have a role in modulating the effects of β-adrenergic stimulation on myocardial contractile and diastolic function, because administration of a PDE5 inhibitor to normal animals led to a depression of the acute inotropic and lusitropic response to dobutamine. This effect did not occur in the animals with heart failure, which suggests that the change in location of PDE5 within the cell was accompanied by a functional effect. This does not mean that the role of PDE5 in modulating cGMP signaling is necessarily unimportant in heart failure. Further investigations in mice have shown that chronic PDE5 inhibition can suppress cardiomyocyte and left ventricular hypertrophy induced by pressure overload with aortic constriction, while maintaining cardiac function.21 Even after hypertrophy had developed in this model, sildenafil administration led to its reversal and improved contractile function.

The observations in healthy human subjects described in this issue of Circulation begin the translation of this preclinical work to the bedside. Indices of contractility and diastolic function, including peak power index, a load-independent measure of ventricular contractility, were assessed noninvasively in a group of men and women at baseline and during infusion of a moderate dose (5 μg · kg⁻¹ · min⁻¹) of dobutamine for a 5-minute period. β-Adrenergic stimulation, as expected, increased contractility and reduced peripheral resistance. The dobutamine infusion was repeated after the study subjects had received either oral sildenafil or placebo. In the subjects receiving sildenafil, the effect of dobutamine on contractility as measured by the load-independent peak power index was diminished. Sildenafil also diminished the augmentation of left ventricular ejection fraction that resulted from dobutamine, an effect opposite to what might have been expected if the sole effect of PDE5 inhibition was to decrease peripheral afterload. In fact, the decrease in peripheral vascular resistance induced by dobutamine was unchanged by sildenafil, which suggests that the effect of PDE5 inhibition on β-adrenergic stimulation of vascular smooth muscle is less than that of cardiomyocytes. In contrast to the observations of Senzaki et al.,17 sildenafil did not significantly alter the improvement in diastolic function that occurred with dobutamine.

How important are these findings to the cardiologist? These observations illustrate the role of cGMP signaling in cardiomyocyte physiology and confirm the presence of PDE5 in the normal heart and its role in regulating cellular function. The identification of these effects should not alter the current practice of prescribing PDE5 inhibitors for the treatment of male erectile dysfunction, because it appears unlikely that the diminution in cardiac response to adrenergic stimulation should lead to adverse events, even in patients with coronary disease.

Perhaps the more intriguing question raised by the findings of Borlaug et al13 is whether or not the blunting of adrenergic stimulation of the myocardium by PDE5 inhibition will have important effects in patients with cardiac dysfunction who may be using these agents chronically. The canine studies of Senzaki et al17 found that PDE5 inhibition appeared not to alter the response of myocardial function to β-adrenergic stimulation, and this needs to be assessed in heart failure patients as well. Sildenafil does not appear to alter resting cardiac contractility or relaxation in patients with either right19 or left22 ventricular failure, but its effects in these patients when under transient adrenergic stimulation are not yet known. The use of PDE5 inhibitors for the treatment of pulmonary arterial hypertension is expanding, yet this is a group of patients in whom right ventricular contractile function may be insufficient to match the increased afterload present. Will PDE5 inhibition diminish contractile reserve in these patients, or will it serve a beneficial effect to preserve contractile function and inhibit adverse remodeling, much as it does in mice that have undergone aortic banding? Further studies are needed to assess whether or not chronic PDE5 inhibition alters cardiac remodeling in heart failure due to either systolic or diastolic dysfunction, to determine whether its potentially beneficial pulmonary and systemic vascular effects lead to improvements in exercise capacity, and to identify whether this effect is diminished by a reduction in contractile reserve. Studies of PDE5 inhibition in patients with hypertrophic cardiomyopathy and in patients in whom arrhythmias are thought to be exacerbated by increased adrenergic tone may also be fruitful.

Clinicians treating heart failure have been disappointed in the utility of chronic treatment of patients with vasodilators, such as PDE3 inhibitors, that augment the effects of adrenergic stimulation on the myocardium. Perhaps a pulmonary and systemic vasodilator that blunts adrenergic stimulation will be of greater utility.

Disclosure
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Circulation. 2005;112:2589-2591
doi: 10.1161/CIRCULATIONAHA.105.577627
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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Of the molecules that transmit an extracellular message to alter cardiomyocyte physiology, the cyclic nucleotides are among the better understood as regulators of cell function. The relatively recent identification of nitric oxide (NO) as a stimulus of cGMP production by soluble guanylate cyclase, as well as of the natriuretic peptides as a stimulating membrane-bound guanylate cyclase, has led to increasing interest in the study of the effects of modulating intracellular cGMP, with most interest being in the area of vascular biology. Studies of the myocardial effects of altering intracellular cGMP have been less extensive, perhaps because systemic agents that affect cGMP levels are often vasodilatory, and their administration is accompanied by changes in blood pressure that can limit the ability to observe myocardial effects. Both cAMP, the second messenger of the β-adrenergic signaling system, and cGMP have a rapid intracellular turnover as a result of the balance between their formation by cyclases and their degradation by phosphodiesterases (PDEs). In this issue of Circulation, Bourlaug and colleagues use load-independent measures of contractility to assess the myocardial effects of an agent (sildenafil) that increases intracellular cGMP levels by inhibiting its degradation.

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In myocardial cells, cGMP has a several intracellular targets that may alter contractility and diastolic function. cGMP can activate a cGMP-dependent cAMP PDE, decreasing myocardial cAMP levels and thereby leading to a reduction of cAMP-dependent phosphorylation of the L-type calcium channels and of calcium influx. cGMP can also depress cAMP production by inhibiting adenylate cyclase. Furthermore, a cGMP-dependent protein kinase can also directly decrease the magnitude of calcium influx through the L-type channels. In addition, a separate cGMP-dependent protein kinase can phosphorylate troponin I, which results in a decreased sensitivity of the contractile apparatus to calcium. The phosphorylation of troponin I is also thought to be the mechanism by which cGMP can accelerate myocardial relaxation, thereby improving diastolic function.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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(Circulation 2005;112:2589-2591.) © 2005 American Heart Association, Inc.
Circulation is available at http://www.circulationaha.org
DOI: 10.1161/CIRCULATIONAHA.105.577627

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