Few intracellular second messengers received more attention in cardiovascular basic and clinical research than cyclic GMP (cGMP). Guanylyl cyclases produce cGMP from its precursor molecule, guanosine triphosphate. Soluble guanylyl cyclase is activated by NO, whereas membrane-bound guanylyl cyclase receptors are activated by natriuretic peptides. Once released, cGMP engages cGMP-dependent protein kinases and ion channels, as well as other downstream targets. Resulting cardiovascular actions include vasodilation, natriuresis, neurohumoral attenuation, platelet inhibition, and improved cardiac remodeling. The action of the released cGMP is terminated through enzymatic breakdown by phosphodiesterases, particularly phosphodiesterase-5. Nonetheless, cGMP interacts also with other phosphodiesterases, some of which are labeled as cGMP inhibitable enzymes, such as the milrinone target, phosphodiesterase 3.

For decades, NO donors, such as organic nitrates or sodium-nitroprusside, were the only available approaches to stimulate the cGMP pathway in patients. The exact mechanism of how these drugs actually work is still controversial. Phosphodiesterase-5 inhibitors were introduced more recently and are widely used in the treatment of erectile dysfunction. Meanwhile, this drug class is also used to ameliorate pulmonary arterial hypertension. Inhaled NO is sometimes used in the intensive care unit. Human recombinant atrial (carpetide) and brain natriuretic peptide (nesiritide) have been tested in patients with acute heart failure with somewhat mixed results. Last year, the Food and Drug Administration approved the direct soluble guanylyl cyclase stimulator, riociguat, for the treatment of pulmonary arterial hypertension. Soluble guanylyl cyclase activators “repairing” the enzyme have been tested in acute heart failure but lowered blood pressure to much in this setting. Endogenous natriuretic peptide levels can be augmented through nepriyisin inhibition. A nepriyisin inhibitor covalently bound to valsartan lowered blood pressure in patients with arterial hypertension. The drug is currently being tested in an outcomes trial in patients with congestive heart failure. A novel engineered natriuretic peptide activating guanylyl cyclase receptors A and B showed a beneficial effect on cardiac fibrosis in rats. Finally, there are other drugs with dual actions, such as the β-adrenoreceptor blocker nebivolol, which also elicits NO release, or novel organic nitrate hybrid molecules.

Given all these developments, it is likely that we will see a variety of cGMP-modulating drugs in the clinic. Some could prove useful in hypertension management. We ought to know more about human cGMP physiology and develop ways to identify patients who are more or less likely to respond to cGMP-modulating drugs. Are there added benefits or risks of cGMP modulation that we have not yet recognized? I suggest that carefully conducted patient-oriented research may provide answers that may have escaped routine preclinical and clinical development.

Okamoto et al tested contributions of NO release to blood pressure reduction with nebivolol in autonomic failure patients. In these patients, the baroreflex feedback loop is interrupted because of efferent sympathetic and parasympathetic dysfunction. The resulting impairment in baroreflex blood pressure buffering makes these patients exquisitely hypersensitive to vasoactive agents including NO-releasing agents. A single nitroglycerin “puff”, which hardly changes blood pressure in a young healthy person, can elicit a profound, potentially dangerous depressor response in autonomic failure patients. In this unique human model, Okamoto et al compared influences of placebo, metoprolol, and nebivolol on supine blood pressure during the night. Both metoprolol and nebivolol are β-adrenoceptor antagonists. In contrast to metoprolol, nebivolol also elicits NO release. Phosphodiesterase-5 inhibition with sildenafil, which augments endogenous cGMP-mediated responses, served as positive control intervention.

Metoprolol treatment did not reduce supine blood pressure during the night. The likely explanation is that in these patients, cardiac sympathetic drive was low to begin with. In contrast, nebivolol elicited a substantial depressor response. The authors attribute this differential response to nebivolol-induced NO release. In another recent study, hypertensive women showed similar reductions in ambulatory blood pressure and responded similarly to sodium loading on metoprolol or on nebivolol treatment. Apparently, blood pressure-lowering effects of drugs augmenting cGMP are unmasked in patients with impaired baroreflex counter-regulation. Such patients are usually older and frail and may be under-represented in clinical trials.

The remarkable hypersensitivity to vasoactive medications in autonomic failure patients also allowed Okamoto et al to obtain further insight in mechanisms determining
cGMP blood pressure responsiveness. In fact, patients showing blood pressure reductions with sildenafil also responded to nebivolol, whereas sildenafil-resistant patients did not respond to nebivolol either. The observation that some patients refuse to respond to, both, nebivolol-induced NO release and endogenous cGMP augmentation through phosphodiesterase-5 inhibition is scientifically and clinically important. There may be a state of cGMP resistance, which could mitigate health benefits across a wide range of cGMP-modulating drugs. Genetic mechanisms may play a role. cGMP-dependent protein kinase, for example, is genetically heterogeneous.\(^1\)

The study by Okamoto et al\(^8\) is a reminder that carefully conducted mechanistic patient-oriented research can provide information that is not obtained during routine drug development. Similarly, the observation that cGMP augmentation through natriuretic peptides profoundly affects human lipid metabolism was shown in small scale academic investigations rather than drug development programs.\(^3\) The numbers of patients included in such studies and the associated costs are typically minuscule compared with clinical trials required for drug development. More mechanistic studies in patients could help targeting the right medication to the right patients and help to identify risks early on. It is worth mentioning through that the underutilized nonpharmacological intervention physical exercise acutely increases natriuretic peptide\(^1\) and endothelial NO release\(^1\) in human beings, thus, increasing cGMP at no additional cost.

**Disclosures**

J. Jordan is a scientific advisor for Novartis, Boehringer-Ingelheim, Orexigen, and Vivus, and exercises regularly.

**References**

Cyclic Guanosine Monophosphate Modulation and Blood Pressure
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