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Right ventricular dysfunction (RVD) afflicts more than half of all heart failure (HF) patients and is the strongest predictor of poor outcomes, independent of left ventricular ejection fraction. The molecular pathophysiology of RVD remains poorly understood and RVD-targeted medical therapy does not yet exist. Cyclic guanosine monophosphate (cGMP), a ubiquitous second messenger in the cardiovascular system, is known to mediate cardioprotective signaling. Animal studies have shown that cGMP enhancement can reverse pathological RV remodeling and improve RV function, though the optimal way to enhance cGMP signaling is unclear. Despite their therapeutic promise, not all cGMP enhancing drugs have been beneficial in HF patients. This clinical inconsistency may reflect: a) disparities in preclinical versus clinical studies and b) nuances in cGMP signaling. Whereas clinical trial subjects overwhelmingly take guideline directed medical therapy (GDMT), heart failure animal models typically do not. Moreover, cGMP is spatially regulated intracellularly by its "sources" (guanylyl cyclases) and "sinks" (phosphodiesterases, PDEs). Local intracellular pools of cGMP have distinct functions; thus, existing cGMP enhancing drugs increase distinct and different cGMP pools. We have identified novel mechanisms of soluble guanlylyl cyclase (sGC) dysregulation in the hypertrophied and failing left ventricle (LV), resulting in altered sGC subcellular localization and blunted cyclase activity. Whether sGC is similarly dysregulated in the failing RV is unknown, and how GDMT alters sGC/cGMP signaling within the dysfunctional RV has not been studied. Our preliminary analysis of cardiac tissue from end-stage HF patients suggests that sGC/cGMP signaling indeed differs between the RV and LV. We hypothesize that sGC/cGMP signaling within the dysfunctional RV varies with the acuity of RVD development and the use of β-blocker and ACE inhibitor, the cornerstones GDMT for HF. We aim to transform the care of patients with RV dysfunction by providing the mechanistic rationale for optimal use of cGMP modifying drugs and the development of novel RVD-targeted therapies.