Mechanisms underlying vasomotor abnormalities and increased peripheral resistance exacerbating heart failure (HF) are poorly understood. To explore the role and molecular basis of myogenic responses in HF, 10 weeks old C57Bl6 mice underwent experimental myocardial infarction (MI) or sham surgery. At 1 to 12 weeks postoperative, mice underwent hemodynamic studies, mesenteric, cerebral, and cremaster artery perfusion myography and Western blot. Organ weights and hemodynamics confirmed HF and increased peripheral resistance after MI. Myogenic responses, ie, pressure-induced vasoconstriction, were increased as early as 1 week after MI and remained elevated. Vasoconstrictor responses to phenylephrine were decreased 1 week after MI, but not at 2 to 6 weeks after MI, whereas those to endothelin (ET)-1 and sphingosine-1-phosphate (S1P) were increased at all time points after MI. An antagonist (JTE-013) for the most abundant S1P receptor detected in mesenteric arteries (S1P(2)R) abolished the enhanced myogenic responses of HF, with significantly less effect on controls. Mice with genetic absence of sphingosine-kinases or S1P(2)R (Sphk1(-/-); Sphk1(-/-)/Sphk2(+/+); S1P(2)R(-/-)) did not manifest...
enhanced myogenic responses after MI. Mesenteric arteries from HF mice exhibited increased phosphorylation of myosin light chain, with deactivation of its phosphatase (MLCP). Among known S1P-responsive regulators of MLCP, GTP-Rho levels were unexpectedly reduced in HF, whereas levels of activated p38 MAPK and ERK1/2 (extracellular signal-regulated kinase 1/2) were increased. Inhibiting p38 MAPK abolished the myogenic responses of animals with HF, with little effect on controls. Rho-independent p38 MAPK-mediated deactivation of MLCP underlies S1P/S1P(2)R-regulated increases in myogenic vasoconstriction observed in HF. Therapeutic targeting of these findings in HF models deserves study.