Dokumenttyp: journal article

Autor(en) des Beitrags: Sun, Xutong; Sharma, Shruti; Fratz, Sohrab; Kumar, Sanjiv; Rafikov, Ruslan; Aggarwal, Saurabh; Rafikova, Olga; Lu, Qing; Burns, Tantiana; Dasarathy, Sridevi; Wright, Johnny; Schreiber, Christian; Radman, Monique; Fineman, Jeffrey R; Black, Stephen M

Titel des Beitrags: Disruption of endothelial cell mitochondrial bioenergetics in lambs with increased pulmonary blood flow.

Abstract: The mitochondrial dysfunction in our lamb model of congenital heart disease with increased pulmonary blood flow (PBF) (Shunt) is associated with disrupted carnitine metabolism. Our recent studies have also shown that asymmetric dimethylarginine (ADMA) levels are increased in Shunt lambs and ADMA increases the nitration of mitochondrial proteins in lamb pulmonary arterial endothelial cells (PAEC) in a nitric oxide synthase (NOS)-dependent manner. Thus, we determined whether there was a mechanistic link between endothelial nitric oxide synthase (eNOS), ADMA, and the disruption of carnitine homeostasis in PAEC. Exposure of PAEC to ADMA induced the redistribution of eNOS to the mitochondria, resulting in an increase in carnitine acetyl transferase (CrAT) nitration and decreased CrAT activity. The resulting increase in acyl-carnitine levels resulted in mitochondrial dysfunction and the disruption of mitochondrial bioenergetics. Since the addition of L-arginine prevented these pathologic changes, we examined the effect of L-arginine supplementation on carnitine homeostasis, mitochondrial function, and nitric oxide (NO) signaling in Shunt lambs. We found that the treatment of Shunt lambs with L-arginine prevented the
ADMA-mediated mitochondrial redistribution of eNOS, the nitration-mediated inhibition of CrAT, and maintained carnitine homeostasis. In turn, adenosine-5′-triphosphate levels and eNOS/heat shock protein 90 interactions were preserved, and this decreased NOS uncoupling and enhanced NO generation. Innovation: Our data link alterations in cellular L-arginine metabolism with the disruption of mitochondrial bioenergetics and implicate altered carnitine homeostasis as a key player in this process. L-arginine supplementation may be a useful therapy to prevent the mitochondrial dysfunction involved in the pulmonary vascular alterations secondary to increased PBF.