Introduction: Atherosclerosis is predisposed at bifurcations, branch points and arterial curvatures where the blood flow is disturbed. Deposition and oxidative modification of low-density lipoprotein (LDL) in the subendothelial intima is an early event in the pathogenesis of atherosclerosis. However, the effect of disturbed flow (d-flow) on LDL oxidation and the underlying mechanisms remain unclear.

Purpose: In this study, we investigated the role of 12/15-lipoxygenase (LOX) in LDL oxidation in endothelial cells (EC) and the development of atherosclerosis at d-flow sites.

Methods: En face immunofluorescence was performed to analyze the expression of 12/15-LOX in EC under exposure to different flow patterns. Protein expression and LDL oxidation was studied in vitro by using 2 different flow apparatuses. Animal model of d-flow was established by partial ligation of the carotid artery.

Results: En face staining exhibited a significant increase in 12/15-LOX protein expression in EC in areas exposed to d-flow than those exposed to steady flow (s-flow). Carotid partial ligation in ApoE knockout mice led to substantially increased deposition of oxidized LDL in the subendothelial intima and formation of atherosclerotic plaques in the carotid artery, whereas these detrimental effects by d-flow were markedly attenuated in ApoE/12/15-LOX double knockout mice. In cultured EC, d-flow generated by a reversal flow pump markedly promoted the expression of 12/15-LOX and translocation of the protein onto the cell membrane. Inhibition of 12/15-LOX in EC, either by knockdown with its specific siRNA or a pharmacological inhibitor, suppressed production of 15s-HETE and LDL oxidation in response to d-flow. Mechanically, we found d-flow induced the expression of 12/15-LOX by activating a specific responsive element in the 12/15-LOX promoter through recruiting a shear stress-sensitive transcriptional factor SREBP2. Chromatin immunoprecipitation further confirmed the interaction of SREBP2 with the promoter of 12/15-LOX upon d-flow exposure.

Conclusions: These data define an essential role of 12/15-LOX in promoting the pathogenesis of atherosclerosis under d-flow by increasing LDL oxidation in EC through SREBP2 signaling.