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SUMMARY
Emphysema is a prominent feature of lung disease related to alpha-1 antitrypsin deficiency (AATD), and related to significant morbidity and mortality. There are currently no medical therapies targeting emphysema with the exception of alpha-1 antitrypsin (AAT) augmentation. Pulmonary microvascular perfusion may play a role in the pathogenesis of emphysema, particularly related to AATD. Platelets are implicated in many vascular diseases and activated platelets are associated with vasoconstriction and inhibited by aspirin. As they are also activated by serine proteases, platelets may be relevant in emphysema associated with AATD, a disease defined by low levels of the serine protease inhibitor AAT. In addition, AAT augmentation therapy is widely used but its benefit has not been definitively proven in a randomized controlled trial (RCT). In a combined analysis of two trials, AAT augmentation was shown to reduce the progression of CT emphysema. In animals, AAT has been shown to reduce endothelial apoptosis and emphysema. Therefore, aspirin may reduce vasoconstriction, and AAT augmentation may reduce endothelial apoptosis in humans; however, it is unknown whether either treatment can improve pulmonary perfusion or decrease CD31+ endothelial microparticles (EMPs), which are reflective of endothelial apoptosis.

In this application, we propose to recruit 15 subjects with PiZZ AATD on augmentation therapy to perform a cross-over RCT of aspirin compared to placebo to test the hypothesis that aspirin improves pulmonary microvascular blood flow measured on contrast-enhanced pulmonary MRI, and reduces CD31+ EMPs. In the same 15 subjects, we will also perform an observational study comparing on AAT augmentation (the placebo arm of cross-over study) to the same subjects off AAT augmentation (after 5 weeks without AAT), to test the hypothesis that AAT augmentation therapy reduces CD31+ EMPs and improves pulmonary microvascular blood flow.

Confirmation of these hypotheses would suggest that aspirin may improve pulmonary microvascular perfusion in AATD-associated lung disease, prompting Phase IIb/III RCTs of aspirin in pulmonary perfusion and emphysema, provide evidence of novel effects of AAT augmentation and support the use of these innovative biomarkers for testing other perfusion or endothelial-related therapies in AATD.