the main contribution will come from more careful surgical manipulation, respecting the "sensitive" pulmonary veins.

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Commentary: The dam, the river, and the riverbank—Should we look at pulmonary vein obstruction from a different perspective?

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CENTRAL MESSAGE

Pulmonary vein obstruction is a lethal disease without effective therapy. We are looking for new treatments, such as the rapamycin patch, but we probably miss the overall picture to be successful.

Pulmonary vein obstruction (PVO) may occur as a primary congenital disease or as a complication of total anomalous pulmonary vein return surgical repair. In both forms, when the disease acquires the malignant characteristics of upstream progression,[1] there are no effective therapies able to change its lethal fate. The disease mechanism and progression have been thoroughly explored with a large animal model that reproduces the disease progression.[2]

In this issue of the *Journal*, Masaki and colleagues[3] report on their proposed new large animal model than encompasses a surgical suture of the left lower pulmonary vein. They elegantly designed a study to understand the disease mechanism, which they divided into two experiments. First, they set up the model and identified a possible treatment target. Second, they evaluated the treatment effect by inhibition of the identified target. Interestingly, they found that PVO is driven mainly by the dedifferentiation of smooth muscle-like cells and activation of mammalian target of rapamycin (mTOR) pathway.[3]

Their findings seem different from the other proposed mechanisms, such as the endothelial to mesenchymal transition and transforming growth factor β_1 pathway activation.[2,4] They are not contrary to what has been previously reported, however, and their newly described activation pathway should be interpreted as another process activated in PVO disease. Masaki and colleagues[1] propose the application of a rapamycin (mTOR pathway blocker) patch at the anastomotic site to reduce the PVO

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progression. Rapamycin at high dose slowed down PVO progression in the first week and a determined a longer time of pulmonary vein complete occlusion compared with the untreated group. The findings are extremely interesting but weakened by some study limitations with respect to how the effect of rapamycin was assessed. Evaluation of obstruction was based on weekly cardiac catheterization, without a histologic specimen to support the delay of obstruction with molecular data. Secondarily, rapamycin is completely released after 4 weeks from its application, but specimen samples were harvested at 8 weeks, leaving the disease to reactivate and progress for the remaining 4 weeks. These two major limitations allow us to observe only that rapamycin slows the disease, without any histologic supportive data. We should use a common definition classification and models[5] to be able to test the efficacy of a proposed new treatment and international coordination is recommended among the different groups studying the disease.

Still, it is not clear to me how PVO starts. Is the turbulent blood hitting and activating the endothelium? Is the wall-shear stress triggering smooth muscle proliferation? Which process comes first? We should probably look at PVO from a broader perspective as a hydrogeologic process and study the dynamic impact of stenosis (the dam) and evaluate the role of blood flow forces (the river) on pulmonary vein tissue (the riverbank).This approach may help to delineate the PVO disease because its initial stages with a clear definition of all pathways and tissue layers will be activated. The identification of such an early-phase disease trigger will probably be the real therapeutic target that will make our surgical strategies or medical treatment effective because, when the PVO starts, it does not stop. In conclusion, this is an important study that opens a new field of investigation and a potential treatment target for PVO, with some promising results that will, it is to be hoped, have future confirmation.

CONG

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