Renin-Angiotensin System in Aortic Aneurysm

Still Adding Puzzle Stones to an Anything but Complete Picture

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Despite significantly improved techniques for surgical intervention, aortic aneurysms still remain a disease with a high rate of mortality (caused by rupture), sadly often affecting patients at young age.[1] Death also frequently happens in patients, who already underwent aortic surgery, and the surgical procedure as such has a relatively high mortality risk, too. For these reasons, a pharmacological treatment, which delays progression of the disease, postpones the need for surgical intervention and protects from aortic rupture is a highly unmet medical need.

In this issue, Lange et al[2] provide evidence that stimulation of the angiotensin AT2 receptor delays progression of abdominal aortic aneurysms in rats by prevention of extracellular matrix degradation and preservation of vascular integrity.

This study is an addition to several previous preclinical and also clinical studies, which explored the effectiveness of pharmacological interference with the renin-angiotensin system (RAS) in aortic aneurysms.[3,4] This approach is based on a multitude of data showing the involvement of the RAS in the pathogenesis of aortic aneurysms, regardless, whether aneurysms are located in the thoracic or abdominal aorta.[3]

The equal involvement of the RAS in both types of aneurysm is somewhat surprising because thoracic aortic aneurysms (TAA) and abdominal aortic aneurysms (AAA) differ in many other ways (Figure).[1] TAA develop mainly in the ascending part of the aorta, are usually caused by genetic defects affecting the connective tissue (eg, mutations in the gene for fibrillin-1 causing Marfan syndrome), have no sex preference, often already develop in young people or even children, and are complicated by dissection.[1,3] In contrast, AAA typically occur in the aorta distal of the renal arteries with a preference of males of older age and smoking as a primary risk factor.[1,3]

Despite these differences, the pathogenesis of both, TAA and AAA, seems to involve an overactivated RAS resulting in excessive AT_1R (angiotensin AT1 receptor) stimulation and subsequent activation of TGFβ (transforming growth factor β) signaling.[3] Notably, TAA and AAA can both be induced by Ang II infusion; however, the resulting pathology differs in that AAA is easier to induce in male than in female animals (which mirrors the human situation), and only the pathology of AAA involves neovascularization of aneurysmal tissue. Moreover, although histological changes in TAA are more concentric, in AAA, the changes are rather focal.[3]

The proven involvement of the RAS in the pathophysiology of AAA and TAA has led to several attempts to test pharmacological interference with the RAS to achieve a delay in disease progression.

The conventional approach of RAS interference is the prevention of excess AT_1R stimulation by AT_1R blockers (ARBs), angiotensin-converting enzyme inhibitors or renin inhibition. All of these approaches have been tried successfully for different AAA and TAA models by various groups including the authors of the present article.[4,5] There is only one published negative study by te Riet et al with aliskiren in TAA (fibulin-$4^{R/R}$ mice), which at the same time also showed a lack of effect of β-adrenergic receptor blockade (propranolol; β-blockers are still standard treatment of AAA/TAA), but a positive treatment effect of an ARB (losartan).[6] Because in this study, only RAS interference, which promotes indirect stimulation of the unopposed AT_2R (angiotensin AT2 receptor) by reactively elevated levels of Ang II (ie, AT_1R blockade by Losartan), but not RAS interference, which mitigates AT_2R stimulation (ie, renin inhibition by Aliskiren), was therapeutically effective, the authors concluded that indirect AT_2R stimulation may be essential for successful RAS interference for the treatment of aortic aneurysms.

In 2 publications in *Science*, Habashi et al[7] demonstrated in $Fbn1^{C1039G/+}$ mice, a model of Marfan syndrome–associated TAA, that a 10-month treatment with the ARB losartan, which started with treating the unborn pups by applying the drug to their mothers from 2 weeks of gestation, completely prevented aortic dilatation, elastic fiber fragmentation, and aortic wall thickening. In the second publication, they then showed that the protective effect of losartan on aneurysm development and the inhibition of TGFβ signaling, which is thought to be an essential mechanism of action, is lost when the AT_2R is knocked out in the $Fbn1^{C1039G/+}$ mice.[8]

These studies encouraged researchers and clinicians to test AT_1R blockade clinically (which will be discussed further

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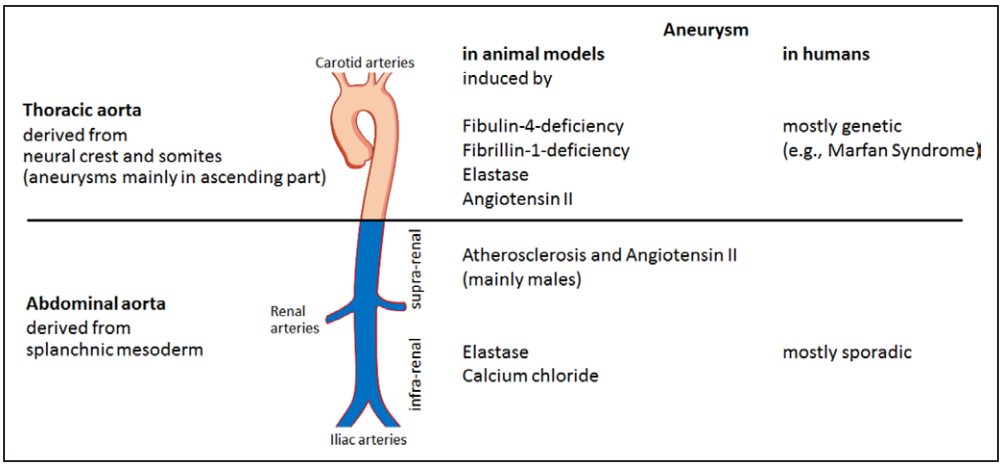

Figure. Thoracic and abdominal aortic aneurysms. The smooth muscle layers of the thoracic and abdominal aorta are derived from different lineages during development. Therefore, aneurysms observed in these 2 parts of the vessel have distinct pathogenesis and are induced by different genetic or pharmacological stimuli.

below), but it was also an incentive for Lange et al[2] to test direct instead of indirect AT_2R stimulation in a preclinical model of aortic aneurysm. In contrast to the studies by Habashi et al and te Riet et al in TAA models, Lange et al[2] performed their study in a model of elastase-induced AAA in rats and indeed found a protective effect of direct AT_2R stimulation (2-week treatment with Compound 21 [C21] starting immediately after aneurysm induction).

Interestingly, in April this year, a study by Verbrugghe et al[9] was published, which investigated a potential preventive effect of direct AT_2R stimulation with C21 in $Fbn1^{C1039G/+}$ mice (TAA/Marfan syndrome model), the same model used by Habashi et al and te Riet et al.[6–8] Treatment of mice for 6 months with C21 starting at the age of 8 weeks had no effect on the progression of TAA when compared with vehicle-treated mice, nor had treatment with enalapril or losartan, combined or not with C21.[9]

Because of the heterogeneity of models and protocols, it is currently hard to decide, why AT_2R stimulation attenuated AAA, but not TAA, formation, whereas ARBs resulted in more consistent efficacy in TAA and AAA.

Eventually, the true value of the animal studies will be decided by the translatability into the clinical situation. The encouraging preclinical studies with ARBs have already been the incentive for many clinical studies, which also started with encouraging results. In 2008, Harry Dietz's group published a retrospective analysis of data from 18 pediatric patients with Marfan syndrome, who had been put on an ARB, because other treatments failed to delay aneurysm formation. Change to an ARB in these patients led to a significant reduction of aortic root dilatation.[10] However, in a subsequent randomized trial in children and young adults with Marfan syndrome, losartan was not more effective than atenolol with regard to aortic root enlargement.[11] Although this result was disappointing, it did not really rule out a treatment effect of losartan or even superiority in comparison to atenolol because (1) the study had no placebo group, (2) aortic root dilatation was comparable to the losartan group in the retrospective analysis mentioned above (which showed a treatment effect compared with placebo),[10] and (3) the dose of losartan was relatively low—likely too low for yielding sufficient indirect AT_2R stimulation. The results of further, much better powered clinical studies are eagerly awaited.[12]

The clinical relevance of the study by Lange et al[2] may be debated because it used a prevention protocol in a model of AAA with known limited translatability.[13] Therefore, more preclinical and eventually clinical studies will be needed to finally decide whether AT_2R stimulation may be a promising new therapeutic concept for the treatment of AAA and TAA or not.

Disclosures

U.M. Steckelings is currently employed part-time by Vicore Pharma and received modest research support (free drug supply; financial support for attending conferences) from Vicore Pharma. The other author reports no conflicts.

References

1. Wilson NK, Gould RA, Gallo MacFarlane E, Consortium ML. Pathophysiology of aortic aneurysm: insights from human genetics and mouse models. *Pharmacogenomics*. 2016;17:2071–2080. doi: 10.2217/pgs-2016-0127.
2. Lange C, Sommerfeld M, Namsolleck P, Kintscher U, Unger T, Kaschina E. AT_2R (angiotensin AT2 receptor) agonist, compound 21, prevents abdominal aortic aneurysm progression in the rat. *Hypertension*. 2018;72:XXX–XXX. doi: 10.1161/HYPERTENSIONAHA.118.11168.
3. Lu H, Rateri DL, Bruemmer D, Cassis LA, Daugherty A. Involvement of the renin-angiotensin system in abdominal and thoracic aortic aneurysms. *Clin Sci (Lond)*. 2012;123:531–543. doi: 10.1042/CS20120097.
4. Xu B, Xuan H, Iida Y, Miyata M, Dalman RL. Pathogenic and therapeutic significance of angiotensin II type I receptor in abdominal aortic aneurysms [published online ahead of print January 22, 2018]. *Curr Drug Targets*. doi: 10.2174/1389450119666180122155642. http://www.eurekaselect.com/159269/article.
5. Kaschina E, Schrader F, Sommerfeld M, Kemnitz UR, Grzesiak A, Krikov M, Unger T. Telmisartan prevents aneurysm progression in the rat by inhibiting proteolysis, apoptosis and inflammation. *J Hypertens*. 2008;26:2361–2373. doi: 10.1097/HJH.0b013e328313e547.
6. te Riet L, van Deel ED, van Thiel BS, Moltzer E, van Vliet N, Ridwan Y, van Veghel R, van Heijningen PM, Robertus JL, Garrelds IM, Vermeij M, van der Pluijm I, Danser AHJ, Essers J. AT1-receptor blockade, but not renin inhibition, reduces aneurysm growth and cardiac failure in fibulin-4 mice. *J Hypertens*. 2016;34:654–665.
7. Habashi JP, Judge DP, Holm TM, et al. Losartan, an AT1 antagonist, prevents aortic aneurysm in a mouse model of Marfan syndrome. *Science*. 2006;312:117–121. doi: 10.1126/science.1124287.
8. Habashi JP, Doyle JJ, Holm TM, Aziz H, Schoenhoff F, Bedja D, Chen Y, Modiri AN, Judge DP, Dietz HC. Angiotensin II type 2 receptor signaling

attenuates aortic aneurysm in mice through ERK antagonism. *Science*. 2011;332:361–365. doi: 10.1126/science.1192152.
9. Verbrugghe P, Verhoeven J, Clijsters M, Vervoort D, Schepens J, Meuris B, Herijgers P. The effect of a nonpeptide angiotensin II type 2 receptor agonist, compound 21, on aortic aneurysm growth in a mouse model of Marfan syndrome. *J Cardiovasc Pharmacol*. 2018;71:215–222. doi: 10.1097/FJC.0000000000000560.
10. Brooke BS, Habashi JP, Judge DP, Patel N, Loeys B, Dietz HC III. Angiotensin II blockade and aortic-root dilation in Marfan's syndrome. *N Engl J Med*. 2008;358:2787–2795. doi: 10.1056/NEJMoa0706585.
11. Lacro RV, Dietz HC, Sleeper LA, et al; Pediatric Heart Network Investigators. Atenolol versus losartan in children and young adults with Marfan's syndrome. *N Engl J Med*. 2014;371:2061–2071. doi: 10.1056/NEJMoa1404731.
12. Pitcher A, Emberson J, Lacro RV, et al. Design and rationale of a prospective, collaborative meta-analysis of all randomized controlled trials of angiotensin receptor antagonists in Marfan syndrome, based on individual patient data: a report from the Marfan Treatment Trialists' Collaboration. *Am Heart J*. 2015;169:605–612. doi: 10.1016/j.ahj.2015.01.011.
13. Sénémaud J, Caligiuri G, Etienne H, Delbosc S, Michel JB, Coscas R. Translational relevance and recent advances of animal models of abdominal aortic aneurysm. *Arterioscler Thromb Vasc Biol*. 2017;37:401–410. doi: 10.1161/ATVBAHA.116.308534.

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