

Marfan and Sartans: time to wake up!

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This editorial refers to ‘Marfan Sartan: a randomized, double-blind, placebo-controlled trial’[†], by O. Milleron et al., on page 2160.

Marfan syndrome (MFS) is a pleiotropic inheritable connective tissue disorder with its main manifestations in the ocular, skeletal, and cardiovascular organ systems.¹ Life expectancy—largely determined by aortic complications—has significantly increased over the last decades, mainly thanks to improved diagnostics, increased awareness, and prophylactic aortic root surgery. Strategies for medical treatment aimed at reducing the risk for aortic dissection and delaying the time to elective surgery have been developed and were initially mainly based on interfering with haemodynamics.

The majority of MFS patients harbour mutations in the fibrillin-1 gene (*FBN1*), encoding the extracellular matrix protein fibrillin-1, a major constituent of the microfibrils, which provide structural support in many tissues, including the aorta. Studying the role of fibrillin-1 has led to a better understanding of the underlying pathophysiology and has provided new prospects for targeted treatment.

Based on the demonstration of increased transforming growth factor- β (TGF β) signalling in mouse and human tissues of MFS, it was hypothesized that mutations in fibrillin-1 could lead to perturbed sequestration of the inactive TGF β complex.² TGF β was considered as the major culprit—the ‘bad guy’ to tackle. Strategies to pursue this goal were set up with great enthusiasm, which was further enhanced by the initial results in a MFS mouse model and in a small human trial.^{3,4} The exciting news was that TGF β could be adequately inhibited not only by using specific neutralizing antibodies in mice, but also using the tried and tested human drug losartan, an angiotensin II type 1 receptor blocker. In the *Fbn1*^{C1039G/+} mouse model for MFS, treatment with TGF β neutralizing antibodies and losartan showed spectacular results, not only reducing aortic root growth to normal levels but also inhibiting elastic fibre fragmentation in the aortic wall.³ The effect on aortic growth reduction seemed recapitulated in a small non-randomized human study in 18 paediatric MFS patients with a severe phenotype, showing a significant reduction in aortic root growth after adding losartan to conventional treatment.⁴ Expectations were very high following these

publications—not least in the Marfan patient community who were finally given a perspective for ‘cure’.

Now, 10 years later we are awakening from what seems like a dream which was too good to be true and some humility towards the medical, scientific, and—above all—the MFS patient community seems warranted.

The Marfan Sartan study published in this issue is a well-designed double-blind randomized control trial in a large number of MFS patients ($n = 303$, mean age 29.9 years) receiving either placebo or losartan on top of their conventional treatment (beta-blockers in 86% of patients).⁵ After 3 years of follow-up with echocardiography, aortic growth rates at different levels were virtually equal in both groups. No differences in clinical events were noted.

In the large randomized trial published last year, young MFS patients randomized to receive either losartan or atenolol failed to demonstrate superiority of losartan in reducing the rate of aortic root enlargement.⁶ Although these results were already pretty convincing, a glimmer of hope remained that combining losartan with conventional treatment would have a synergistic effect—as was suggested by the small pilot study by Brooke as well as in the open-label COMPARE trial.⁷ With these results of the first double-blind randomized trial by Milleron and colleagues, the high expectations remain sadly unfulfilled and send us back to the drawing board.

Meanwhile, some considerations regarding the losartan studies can be discussed.

- (i) Was the concept of increased TGF β too simplistic? Important progress has recently been made in this field, clearly indicating that TGF β is not simply the ‘bad guy’. The basic concept of altered sequestration has been refuted by demonstrating that a *Fbn1* mouse in which the TGF β binding site was deleted (*Fbn1*^{H1 Δ}) did not present features of MFS.⁸ The role of TGF β in thoracic aortic disease seems to be dimorphic, with a protective role in early developmental stages turning into a marker of a complex disease process later in life.⁹ Careful re-assessment of the pathophysiology led to the hypothesis that altered mechanobiology represents the most common trigger of inherited thoracic aortic disease.⁹ It is now believed that fibrillin-1, along with many other known and unknown

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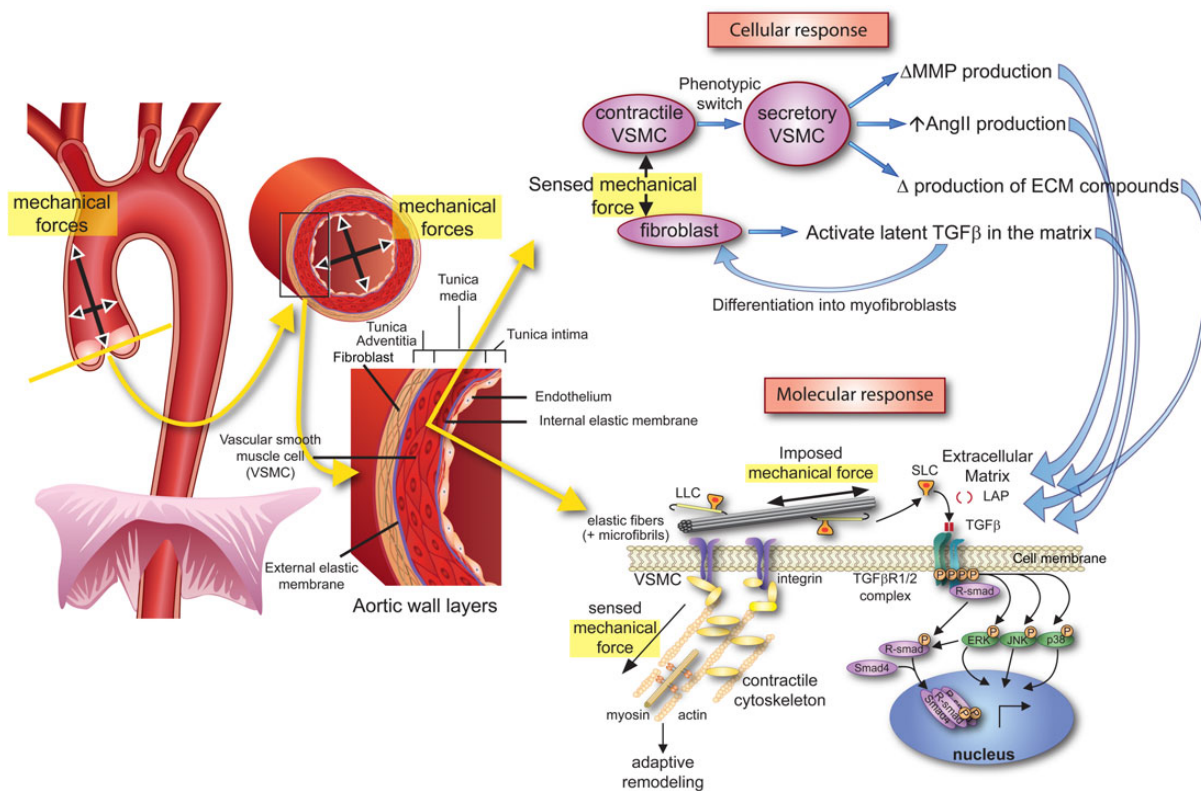


Figure 1 Concept of mechanobiology underlying homeostasis in the thoracic aorta. Alterations, either due to higher imposed forces (hypertension) or due to (genetic) alterations in the various components required for proper sensing and/or transduction of the signal, may lead to aneurysms/dissections. In Marfan syndrome (MFS), mutations in fibrillin-1 affect the mechanical properties of the microfibrils, leading to an altered mechanotransduction signal and initiation of cellular response mechanisms including increased transforming growth factor- β (TGF β) signalling. AngII, angiotensinII; ECM, extracellular matrix; Erk, extracellular signal regulated kinase; Jnk, c-JunNH2-terminal kinase; LAP, latency associated protein; LLC, large latency complex; MMP, matrix metalloproteinase; Smad, mothers against decapentaplegic; SLC, small latency complex; TGF β , transforming growth factor β ; TGF β R, transforming growth factor β receptor; VSMC, vascular smooth muscle cell.

molecules, plays an important role in mechanotransduction from the endothelium and extracellular matrix to the vascular smooth muscle cells. A summary of these mechanisms is provided in Figure 1 and nicely reviewed in Humphrey *et al.*¹⁰ These new concepts may offer new targets for treatment, not least stressing the importance of targeting the mechanical aspects of the disease process—explaining why the standard treatment with beta-blockers has stood the test of time.

- (ii) Was the evidence for losartan as a TGF β inhibitor too weak? This evidence was based on studies in animal models for chronic renal failure and cardiomyopathy.³ We now know that the angiotensin 1 receptor is an important mechanosensor and that the magnitude of the mode of action of losartan on these mechanosensing properties is probably much higher than that on TGF β . This is further evidenced by the observation that treatment with losartan but not with TGF β neutralizing antibodies has a protective effect on the aorta in the *Fbn1*^{mgR/mgR} Marfan mouse model.
- (iii) Did the mouse models fail us? The old cliché of ‘humans are not mice’ is painfully evident from these study results. An intriguing finding in the Habashi trial is the observation that heart rate in

the mice treated with losartan dropped by 15–20%—a finding never observed in humans and possibly indicating a different response in mice. Several other factors play a role, including the fact that the *Fbn1*^{C1039G/+} MFS mouse model may not be representative for all human MFS aortic disease—both from a genotypic and from a phenotypic perspective. Treatment with losartan in the phenotypically more severe *Fbn1*^{mgR/mgR} mouse model showed markedly less spectacular results.⁹ Differences with regards to the response to losartan according to the underlying genotype were suggested in a recent report from a substudy of the COMPARE trial indicating that patients with haploinsufficient *FBN1* mutations are less responsive to losartan.¹¹ Other notable differences between human and mouse studies relate to timing and dosage of the drugs. The losartan dose given to mice was exponentially much higher than the dose given in the human trials—extrapolating this dose to humans would require potentially lethal doses of >1 g/day.

Though the results of this trial are negative, we should look at it from a positive angle. Even more than before, we need to search for solid evidence for the suggested pathophysiological processes in a

first step. Strategies aimed at new treatment targets need to be carefully developed and reproduced in a pre-clinical setting and should pass every step necessary for clinical trial development. A final crucial question that remains alarmingly unanswered in the context of MFS is what is the 'natural evolution' of aortic diameters in various subsets of MFS patients. Interpretation of study results will remain unreliable in the absence of this knowledge, and collaborative efforts should be undertaken to tackle this shortcoming. For the time being, interference with the mechanical component of mechanobiology using beta-blockers remains the preferred treatment strategy in MFS.

Disclosure

I participated as an investigator in the PHN Marfan trial published in the NEJM 2014.

Conflict of interest: none declared.

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