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Kidney and heart: TGFβ1-mediated cross-talk

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Rzeźnik et al. [1] in their recent paper published in 'Kardiologia Polska' found that revascularisation of unilateral or bilateral renal artery stenosis (RAS) leads to improvement in several echocardiographic parameters reflecting heart structure and function, as well as impacts on plasma transforming growth factor β1 (TGFβ1) and B-type natriuretic peptide. At least some of the effects on the heart (such as LVMI reduction) did not depend on the degree of blood pressure lowering. As can be concluded from the publication, patients did not suffer from symptomatic heart failure (HF; at least in NYHA class III–IV); however, it has been demonstrated recently that RAS revascularisation may also be associated with improvement in NYHA class and reduction in the risk of hospitalisation for HF in patients with concomitant RAS and HF [2].

The message delivered by this paper is very important for both nephrologists and cardiologists. TGFβ1 remains one of the key profibrotic growth factors in renal pathology. It is produced by damaged mesangial cells in the glomerulus (and is crucial for the development of glomerular sclerosis), injured tubular cells and resident interstitial fibroblasts (resulting in interstitial fibrosis). HF in the course of atherosclerotic RAS may develop according to least three different scenarios: (1) Both HF and RAS are consequences of the same, devastating, pathology, namely advanced atherosclerosis; (2) RAS contributes to heart remodelling and dysfunction due to significantly elevated and difficult-to-control hypertension; (3) Humoral mediators released from injured (ischaemic) renal parenchyma may remotely damage the heart (and this may be the case with TGFβ1). The role of TGFβ1 in the development of several heart diseases resulting in myocardial fibrosis has been well recognised for some years [3]. Experimental data suggest that RAS triggers the synthesis and release of several inflammatory and vasoconstrictive agents from the kidney, in addition to the activation of the renin–angiotensin–aldosterone (RAA) axis. These include, among others, endothelin, interleukin-6, TNFα and TGFβ1. It has been demonstrated that disruption of the Smad3 protein gene (signalling pathway essential for TGFβ1 effects) prevents fibrosis of the kidney supplied by stenotic artery even if stenosis persists [4]. Infusion of endothelial progenitor cells into the artery with stenosis significantly decreases plasma levels of several proinflammatory cytokines, prevents myocardial damage and remodelling, even in stenosis remains uncorrected and there is no change in systemic blood pressure [5]. TGFβ1 is one of the key effector molecules involved in epithelial-to-mesenchymal transition, the process of phenotypic change of epithelial tubular cells into fibroblast-like cells — now considered one of the most important mechanisms that lead to kidney fibrosis. A similar process has also been described for cardiac endothelium and was called 'endothelial-to-mesenchymal transition' (Endo-MT) [6].

These and other findings should lead to caution when interpreting apparently 'negative' trials published recently on RAS which did not demonstrate any substantial benefit associated with renal artery revascularisation ± stenting vs. medical therapy — effects on blood pressure and/or kidney function were exactly the same in both types of intervention. Now it is tempting to speculate that successful RAS revascularisation might be a much more definite strategy compared to everyday use of RAA axis blockade in lowering TGFβ1 and thus in limiting the impact of this growth factor on the heart and the kidneys. It seems however plausible to expect some lag time between intervention and expected cardiac benefits, not necessarily apparent in the short time following intervention. The findings of Rzeźnik et al. [1] may hold some promise for more delayed, but possible, benefit following RAS revascularisation for the heart, and possibly for the kidneys.

Conflict of interest: *none declared*

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