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Review article

# Renal studies provide an insight into cardiac extracellular matrix remodeling during health and disease

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ABSTRACT

The remodeling of a heart ventricle after myocardial infarction involves numerous inflammatory mediators that may trigger a long-lasting and a highly fibrogenic process. Likewise, in the kidney, acute and chronic injuries may lead to abnormal extracellular matrix deposition and eventually lead to the loss of renal function. Major breakthroughs have emerged during the last ten years with respect to the pathophysiology of matrix remodeling. Epithelial and endothelial cells are plastic, and able to engage in epithelial (or endothelial)-to-mesenchymal transition (EMT or EndMT), thus actively contributing to the fibrogenesis. Members of the fibrinolytic system were demonstrated to possess unsuspected properties and interact with receptors and integrins on endothelial and epithelial cells. Finally, a notion that stem cells could integrate into damaged tissue has recently emerged, which likely contributes to the tissue repair. In many aspects, the kidney and the heart share many common injury mechanisms. We envision that some of them will be accessible as common therapeutic targets in the future.



**Contents**



## 1. Introduction

Combined renal and cardiac insufficiency is frequent [1,2]. In patients with heart condition, superimposed kidney failure has severe prognostic implications [3] and, vice-versa, the majority of patients with kidney disease will die from cardiovascular complications [4]. Obviously enough, the sodium and water retention that accompanies severe renal failure represents a burden for the ventricles, and even earlier in the course of kidney diseases, the altered glomerular filtration rate is responsible for the accumulation of many undesirable substances that will eventually increase the risk for cardiovascular diseases (Fig. 1). Still, the possibility that more fundamental pathways are at stake, including at the subcellular level, is rarely considered. Considerable data have however accumulated over the last two

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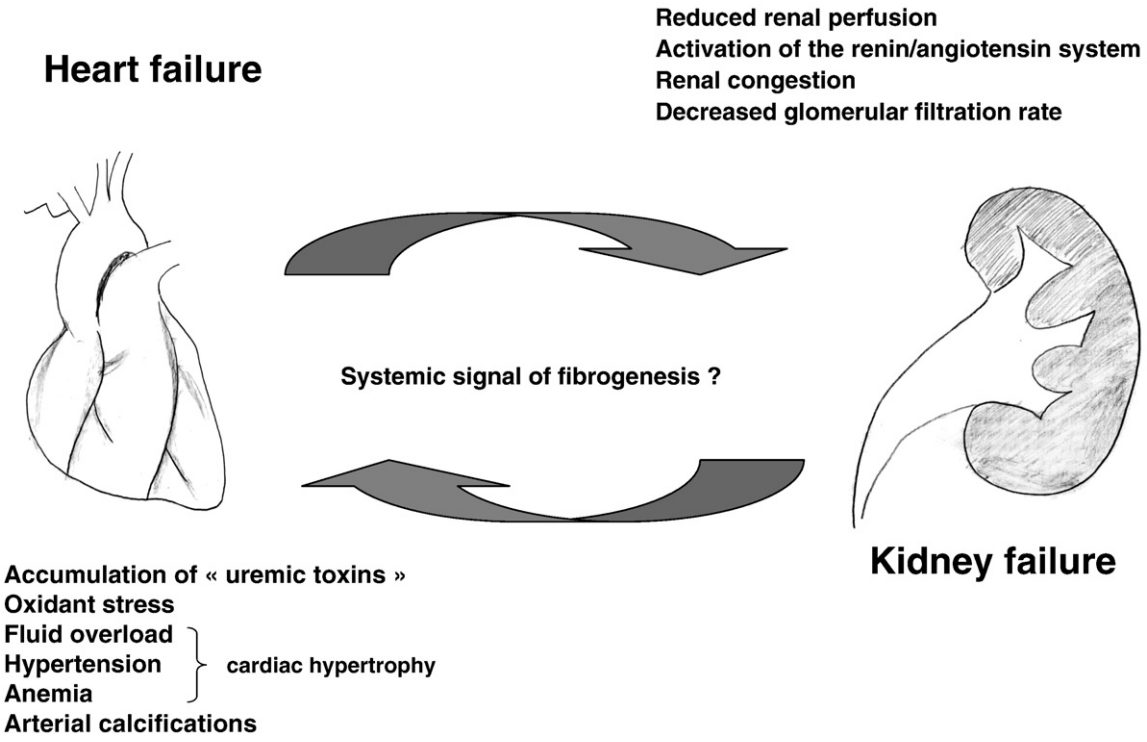


**Fig. 1.** Pathophysiological interactions between heart and kidney. Heart and kidney failures impact on each other, but beyond the well-known mechanical and metabolic interactions depicted here, endothelial and epithelial cells could share a predisposition to engage into a fibrogenic process, at the intra-cellular level. The possibility also exists that, after an injury of one organ, systemic signals are being transmitted to the others.

decades that support the idea that, in both organs, the beneficial effect of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, as an example, goes well beyond their hemodynamic properties, and also relates to their interference with mutually shared intra-cellular signaling pathways [5,6]. Our goal here is to outline that the mechanisms involved in the remodeling of extra-cellular matrix that occurs after acute or chronic kidney injury, are of interest for the understanding of the remodeling of the left ventricle after myocardial infarction. It is indeed probable that the pharmaceutical or cellular tools that are currently designed to temper the fibrogenic response to a chronic condition will not be organ (kidney) specific.

## 2. Ischemia and inflammation trigger an abnormal epithelial response in both organs

Nowadays, on the short term, most patients will survive a myocardial infarction as long as they reach the hospital. However, ischemia leads to the activation of an inflammatory reparative process, which eventually leads to heart fibrosis and organ dysfunction in a persistently high proportion of cases [7]. In the kidney world, ischemic events are also very frequent but two major differences should be mentioned: the acute tubular necrosis usually follows a transient drop in blood pressure and not the clotting of a renal artery, and second, the tubular epithelium shows a high quality of repair [8], so that in the absence of fatal multi-organ dysfunction, the majority of patients will have recovered their anterior renal function by a couple of weeks. In the long-lasting inflammatory context of kidney transplantation, the cold ischemia time is of very bad prognostic value, though [9]. The superimposed inflammation, if chronic and unopposed, might thus be critical after an ischemic insult, either in the heart or in the kidney, through the liberation of many mediators that will harm the tissue with time. In the heart, pro-inflammatory cytokines like TNFα, IL-1 and IL-6 are activated even earlier than the renin angiotensin system following the stroke [10]. Based on *in vitro* evidence, these cytokines supposedly account for the concomitant increase in matrix metalloproteinase (MMP) synthesis and activity by myocardiocytes, fibroblasts and inflammatory cells. Since several animal models reported that MMPs are central in ventricle remodeling (and the same is true in the kidney [11,12]), the pathway from ischemia to fibrosis could be seen as trivial. The reason why this healing and highly fibrogenic response persists in the heart and goes unopposed with time is however unclear. The quality of the underlying vascular bed could be key in the control of the repairing process after a brutal drop in blood flow: in the heart, how invasive they are, in 2009 surgical bypasses still provide the best outcome in patients with severe coronary heart disease [13], maybe because it allows a better revascularization, and in the kidney, benign chronic ischemic nephropathy is increasingly recognized as a cause of end-stage renal disease [14]; also, aging hampers the chances to recover from acute tubular necrosis [15]. Thus, while the heart and the kidneys probably have the potential to recover *ad integrum*, the fibrogenic tonus in both tissues could be critically influenced by the residual ischemia following (or not) an acute injury. To better understand this ongoing fibrogenesis in the heart as in the kidneys, 1) the origin of the fibroblasts has to be elucidated, 2) the reason(s) for their activation should be apprehended and 3) the events occurring at the surface of tubular epithelial cells should be further studied.

## 3. The origin(s) of interstitial fibroblasts

The extra-cellular matrix proteins that progressively invade the tissues and compromise their function are produced by activated fibroblasts, called myofibroblasts [16]. Their origin has been vividly debated during the last decade [17], and the belief that they were only resident, activated, fibroblasts has been challenged in many renal models. Observing microscopic lesions in the biopsies from patients with chronic renal disease, a striking feature is almost