Myocardial fibrosis in chronic kidney disease: potential benefits of torasemide

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Interstitial and perivascular fibrosis is a constant finding in heart biopsies and necropsy studies in patients with chronic kidney disease and hypertension, namely in those with left ventricular hypertrophy. Fibrosis is the result of the unbalance between exaggerated collagen synthesis and unchanged or depressed collagen degradation. A number of factors linked to hypertension and the progressive deterioration of renal function may facilitate such an unbalance. Patients with chronic kidney disease and hypertension are prone to develop diastolic heart failure, and myocardial fibrosis has been suggested as a major determinant of disturbances in diastolic function in these patients. Thus, the therapeutic strategies aimed to reduce cardiac fibrosis may provide a particular cardioprotective benefit in patients with chronic kidney disease. In this regard, recent data suggest that the loop diuretic torasemide reduces myocardial fibrosis and ameliorates cardiac function in patients with chronic heart failure through local mechanisms beyond its effects on the renal excretion of fluid and electrolytes and systemic hemodynamics.

Kidney International (2008) **74** (Suppl 111), S19–S23; doi:10.1038/ki.2008.512

KEYWORDS: arterial hypertension; left ventricular hypertrophy; myocardial remodeling; fibrosis; heart failure; torasemide

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MYOCARDIAL REMODELING IN CHRONIC KIDNEY DISEASE

General aspects

The three lesions constitutive of the structural remodeling of the myocardium (e.g., cardiomyocyte hypertrophy, myocardial fibrosis, and thickening of the intramural arteries and arterioles) are a constant finding in heart biopsies and necropsy studies in patients with chronic kidney disease (CKD), namely in those with arterial hypertension and left ventricular (LV) hypertrophy.[1,2]

Myocardial fibrosis is the consequence of an excessive accumulation of collagen fibers, mainly type I, within the interstitium and around the intramyocardial arteries and arterioles (Figure 1).[3] The accumulation of collagen type I fibers is the result of the imbalance between its exaggerated synthesis by cardiac fibroblasts and myofibroblasts, and its unchanged or depressed degradation by extracellular matrix metalloproteinases.[3] A number of mechanical and humoral factors stimulated during the development and progression of CKD may be responsible for such an imbalance. The clinical evidence available suggests that whereas some of these factors start to operate already from the initial stages (e.g., hemodynamic overload, oxidative stress, inflammation, excess of cytokines such as cardiotrophin-1 and transforming growth factor-β_1 or TGF-β_1), others act preferentially in more advanced stages of CKD (anemia, hyperphosphatemia, excess of parathormone, vitamin D deficit, and uremic toxins).[4] It is likely that synergistic events may occur between the mentioned factors leading to redundant mechanisms of myocardial damage. For instance, initial stimulation in myocardial production of the cardiac growth factor cardiotrophin-1, in response to the mechanical overload imposed by hypertension to the myocardium,[5] may further increase in response to anemia-related myocardial hypoxia.[6]

Clinical impact

The prevalence of LV hypertrophy and diastolic dysfunction is higher in patients with CKD than in patients without CKD, and it increases as CKD progresses (Figure 2).[7–10] One mechanistic explanation for this association can be that CKD facilitates the development of myocardial fibrosis, which in turn, impairs LV diastolic filling.[11] In fact, it has been reported that myocardial fibrosis, as assessed with

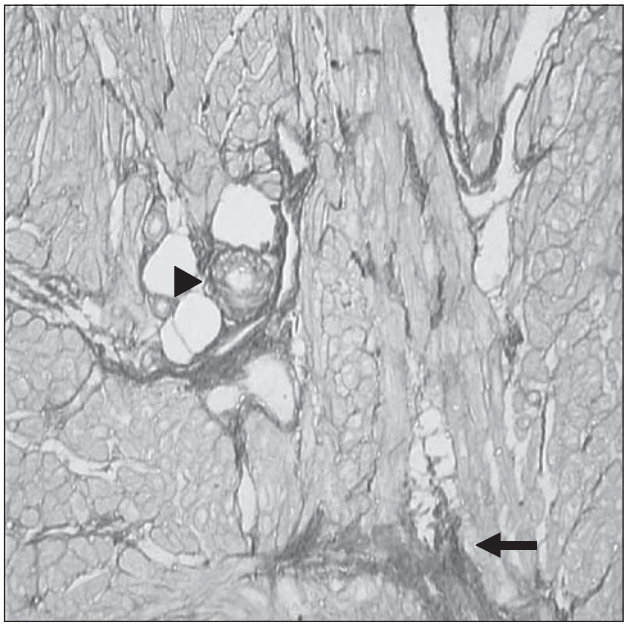

Figure 1 | Myocardial fibrosis in chronic kidney disease. Microscopic image of the myocardium of a patient with stage 3 chronic kidney disease, arterial hypertension and left ventricular hypertrophy showing interstitial (arrow) and perivascular (arrowhead) deposition of collagen fibers stained with picrosirius red. (Original magnification × 20.)

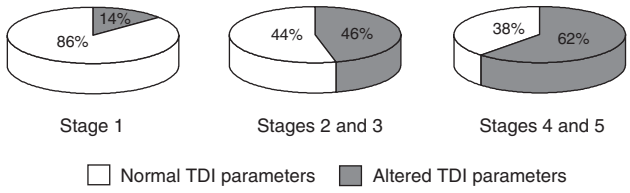

Figure 2 | Diastolic dysfunction in chronic kidney disease. Prevalence of diastolic dysfunction, as assessed by tissue Doppler imaging, in the different stages of chronic kidney disease. TDI, tissue Doppler imaging. (Adapted from de Almeida *et al.*[10])

endomyocardial biopsy,[4] echocardiography with integrated backscatter,[12,13] magnetic resonance imaging,[14] and serum biomarkers of collagen type I deposition,[12,13,15] is higher in hypertensive patients with CKD compared with hypertensive patients without CKD. Furthermore, the severity of fibrosis increases with the stage of CKD.[4] Myocardial fibrosis has been shown to be associated with increased LV stiffness in hypertensive patients,[16] and it has been recently shown that increased stiffness determines augmented LV end-diastolic pressure and impaired LV filling in patients with diastolic heart failure (HF).[17]

Recently, it has been reported that LV filling pressure, as estimated by the early mitral inflow velocity to peak mitral annulus velocity (E/E_m) ratio, was abnormally elevated in 62% of patients with stage 5 CKD.[18] It is interesting to note that, during a median follow-up of 48 months, the E/E_m ratio emerged as an independent predictor of all-cause mortality and cardiovascular death in a multivariate Cox regression analysis. In addition, the E/E_m ratio added significant incremental prognostic value for all-cause mortality and cardiovascular death beyond the standard clinical, biochemical, and dialysis parameters and echocardiographic measurements.

In patients with CKD, diastolic HF can be present as severe intolerance to physical exertion, and it may even lead to acute pulmonary edema or sudden intradialysis hypotension in dialyzed patients.[9] In patients with CKD, the mortality from diastolic HF is higher than that from systolic HF with decreased ejection fraction.[19] In addition to being associated with diastolic HF in patients with CKD, hypertensive heart disease is associated with an increased risk for aortic valve dysfunction, ventricular arrhythmias, atrial fibrillation, and worsening of a coexistent coronary heart disease.[20,21]

TORASEMIDE IN PATIENTS WITH CKD

Torasemide is a high-ceiling loop diuretic that has been shown to reduce extracellular fluid volume and blood pressure in hypertensive patients with CKD.[22] In addition, torasemide is the diuretic with the greatest oral bioavailability in advanced stages of CKD.[23] Therefore, torasemide is currently recommended for the treatment of patients with CKD either with preserved or reduced glomerular filtration rate.[24]

Antifibrotic effect of torasemide

Several recent clinical studies have shown that torasemide possesses the capacity to protect the heart through the reduction of myocardial fibrosis. In a report of the prospective Torasemide In Chronic HF study involving 1377 patients with chronic HF, the use of torasemide was associated with a lower mortality than furosemide.[25] Furthermore, it has been reported recently that torasemide improves LV diastolic function in chronic HF patients to a greater extent than furosemide.[26] As both diuretics exert similar renal effects,[27,28] it is likely that torasemide has beneficial effects other than diuresis in patients with chronic HF.

In this regard, we reported recently that long-term treatment with different loop diuretics may have a variable impact on myocardial fibrosis and fibrillar collagen biosynthesis in chronic HF patients.[29] In fact, although torasemide-treated patients showed decreased myocardial collagen accumulation, furosemide-treated patients did not (Figure 3). In addition, a greater improvement of the New York Heart Association functional class and of parameters assessing cardiac function was observed in torasemide-treated patients than in those treated with furosemide. Experimental support to these findings has been provided by studies showing that torasemide, but not furosemide, reduced myocardial fibrosis and improved myocardial function parameters and survival rate in rats with HF secondary to myosin-induced autoimmune myocarditis.[30,31]

Which are the mechanisms involved in the cardiac antifibrotic effect of torasemide? In a recent study, we found