

Left ventricular systolic dysfunction in chronic kidney disease: from asymptomatic changes in geometry and function to overt heart failure

Disfunzione sistolica del ventricolo sinistro nella malattia renale cronica: dalle alterazioni asintomatiche della geometria e della funzione, allo scompenso cardiaco conclamato

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ABSTRACT: *Left ventricular systolic dysfunction in chronic kidney disease: from asymptomatic changes in geometry and function to overt heart failure. G. Cioffi, L. Tarantini, P. Faggiano, G. Pulignano, G. Russo, A. Di Lenarda.*

A bidirectional relationship between kidney and heart function is present in all stages of cardiac and renal disease, from the asymptomatic phase of left ventricular systolic dysfunction to overt heart failure, as well as from the initial reduction of glomerular filtration rate to end-stage kidney dis-

ease, respectively. The simultaneous presence of both diseases has a significant impact on prognosis and requires specific therapeutic strategies. The early recognition of abnormalities of renal and myocardial function may have a relevant influence on management of combination of these conditions.

Keywords: heart failure, end-stage kidney disease, glomerular filtration rate, left ventricular dysfunction.

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Introduction

Left ventricular (LV) systolic dysfunction (LVSD) and chronic renal disease (CKD) repeatedly co-exist due to the increasing age of the general population, the reduction of renal perfusion due to the impairment of systolic cardiac performance and the tailored treatment of both states [1]. These two conditions have common predisposing causes such as hypertension, type 2 diabetes mellitus (T2DM), obesity and atherosclerosis, so that they share the same pathophysiological mechanisms. People with CKD have high rates of cardiovascular events, particularly when proteinuria is present [2, 3], and this condition should be regarded as a coronary heart disease risk equivalent [4]. Furthermore, the negative impact of CKD on clinical outcomes in patients with acute or chronic heart failure (HF) has been clearly identified [5-7], and in those patients in whom CKD coexists with T2DM, the mortality rate is particularly high, above all the cardiovascular one [8].

In this review, we tried to describe the natural history of LV geometry and systolic function of a heart beating in a patient with CKD, starting from the early changes during the asymptomatic phase of cardiac disease to the culmination of overt HF.

Asymptomatic changes in LV geometry and systolic function in CKD

In patients with CKD, LV mass typically increases in a concentric fashion, paralleling the progression of renal dysfunction [9, 10]. Several investigations analyzed LV structure and geometry in these subjects, focusing on the prevalence of traditional hypertrophy (established near to 40%, approximating 75% at the time of dialysis initiation) and on the description of different LV geometric patterns [9-13]. The hemodynamic alterations induced by CKD (increased preload and afterload) certainly play an important role in changing LV geometry, but in point of fact, they explain only in part the development of concentric remodeling/hypertrophy in these patients [14]. Some investigations conducted in patients with CKD, indeed, documented the lack of correlation between echocardiographic findings and blood pressure levels [14, 15] suggesting that additional causes other than hemodynamic abnormalities (including neuro-hormonal stressors and factors inducing myocardial fibrosis and apoptosis) might produce an excess of LV mass [15, 16]. Such behavior, consisting in a myocardial tissue growth

exceeding the hemodynamic needs has been reported by several studies [17-22] and has been called “inappropriate LV mass” (iLVM), assessed as the ratio between observed and predicted LV mass (calculated from stroke work, gender and body size) [23].

iLVM has been found in a significant proportion of patients with arterial hypertension or aortic stenosis and has been associated with unfavorable cardiovascular profile and adverse prognosis [17-22]. Recently, in a specific study aimed to assess the prevalence of iLVM in patients with CKD [24], we investigated 340 subjects without overt cardiac disease (mean age 68 ± 13 years, 37% women), prevalently hypertensives (94%) and one quarter with T2DM, who had a mean estimated glomerular filtration rate (eGFR) of 67 ± 19 ml/min/1.73 m². iLVM was found in 146 of these patients (43%) and in 7 healthy controls (10%; $p < 0.001$). Prevalence of iLVM, as well as LV traditional hypertrophy, paralleled the severity of renal dysfunction ranging from 10% and 43% in stage 1 CKD patients to 100% and 100% in stage 5 CKD patients, respectively. eGFR was 23% lower (57 ± 19 vs 74 ± 16 , $p < 0.01$) in patients with iLVM than in those with appropriate LV mass. Our results were faultlessly in line with those reported by Nardi *et al.* [25] who found in a large group of patient with hypertension a prevalence of iLVM of 53% which was increasingly higher (38 up to 80%) from stage 2 to 5 CKD. In our study [24], beyond lower eGFR, iLVM was closely and positively associated with higher LV relative wall thickness, LV mass index and, in particular, with lower LV midwall shortening. This was not a surprising finding. It is well-known, indeed, that changes in LV geometry towards a concentric fashion are closely related to impairment of LV midwall mechanics which may be lessened even though conventional echocardiographic indexes of chamber function, such as LV ejection fraction (LVEF), remain normal [26, 27]. This condition can be valuably revealed by the assessment of midwall shortening, which identifies early systolic impairment of circumferential LV myocardial fibers (the myocardial compartment mainly deputed to the pump function) [27]. The impairment of midwall shortening is an early and reliable indicator of the transition phase between normal cardiac function and clinically manifest HF [28] as well as a potent predictor of adverse cardiovascular outcomes in patients with hypertension [29], T2DM [30] and in the subsection of patients with chronic HF in whom LVEF is preserved [31]. In our experience [24], prevalence of impairment of midwall shortening was progressively higher (25% up to 42%, 64%, 89% and 100%) from stage 1 to 5 CKD, clearly indicating a extensive presence of subclinical LVSD, beside changes in LV geometry, in most of people with moderate to severe CKD without clinical signs or symptoms of cardiac disease. All these findings provide reasonable enlightenments on the high cardiovascular morbidity and mortality of patients with CKD and, in particular, explain why they are so susceptible to develop HF.

CKD and symptomatic LV systolic dysfunction

The patho-physiological disadvantages of the excessive LV mass growth were well described many years ago in some pioneering experiences conducted on uremic rats [32, 33]. Since that time, it was clear that CKD was a “metabolic” condition inducing LV hypertrophy by a number of hemodynamic and non-hemodynamic mechanisms. Among the latter, those activated by growth factors, proto-oncogenes, plasma noradrenalin, cytokines and angiotensin II play a central role in activating the intracellular processes that accelerate myocardial fibrosis and apoptosis [34], and altered protein synthesis leading to the building of anomalous sarcomeres, as shown by the re-emergence of fetal muscle-specific gene products in deteriorating hearts put through chronic LV overload [35]. What we are describing is just the molecular biology of LVSD, which inexorably leads to a failing heart and to the HF syndrome after an asymptomatic phase lasting a variable time depending on the compensatory capacities of the individual cardiovascular system.

Acute HF and CKD

Some lines of evidences demonstrate the development of acute HF in patients with concomitant CKD is increasing [36, 37] suggesting the existence of several contributory factors beside the patho-physiological mechanisms consequential to CKD mentioned below. Once HF develops, renal hypo-perfusion occurs in a straight line by the reduction of cardiac output, but also indirectly through the activation of several neuro-hormonal mechanisms [38-40]. In this clinical state, the management of pharmacological and non-pharmacological therapy represents a difficult task [40, 41] since the treatment of congestion may aggravate renal function, a complication particularly frequent (ranging from 20 to 29% of patients in various experiences) in acute-stage HF [42-46]. Such a situation is associated with prolonged clinical destabilization and hospital stay, and is a powerful prognosticator of adverse clinical outcome [36, 37, 42-47]. Due to all these reasons, the attention of researchers has been progressively increased in the last years and a lot of experiences have been published on this issue. However, no clinical investigation has been specifically dedicated to the patients with acute HF and concomitant severe CKD in the past. Furthermore, the systematic exclusion of these subjects from the most of the largest therapy-intervention and device trials impacts the results of the meta-analyses (which prevalently have considered middle-aged male patients with many other characteristics far from those of HF patients of the real world), so that few clinical and prognostic information on these patients are available [48]. As a result, we recently defined clinical features and prognostic markers for short and mid-term mortality in patients with severe CKD hospitalized for an episode of acute HF [49] and recruited in the Italian registry “IN-HF Outcome” [50]. In this study [49], we selected the 455 pa-

tients belonging to the lowest quartile of eGFR (mean value 28 ± 9 ml/min/1.73m²). The study demonstrated that: 1) the in-hospital and 1-year mortality rates of these patients were dramatically high (13.6% and 43.5%, respectively), resulting more than two-fold higher than the total population of patients admitted to hospital for an episode of acute HF; 2) cardiovascular etiology of in-hospital and 1-year death was largely prevalent in comparison with other possible causes which were limited to a minority of cases; 3) predictors of in-hospital mortality were an abnormal status of consciousness, older age, hypo-natremia, lower systolic blood pressure and eGFR. These results are in line with those found in patients enrolled in the ADHERE registry [51] and in the OPTIMIZE-HF registry [52, 53], in which in-hospital mortality was 8% and 4%, respectively, and show that the negative impact of CKD on in-hospital outcome is proportional to the degree of CKD. Indeed, although our HF people were selected for having very low eGFR, eGFR itself was one of the strongest independent predictors of in-hospital death, suggesting that no inferior limit exists of renal function for which the prognostic value of eGFR vanished.

A final consideration regards the pharmacological therapy, analyzed in depth by Tarantini *et al.* [54] in the setting of acute HF patients enrolled in the Italian registry "IN-HF Outcome". At hospital admission, patients with moderate-severe CKD were receiving more frequently diuretics, angiotensin converting enzyme-inhibitor (ACEi) or angiotensin receptor blockers (ARBs) than those with normal or mildly impaired renal function. During hospitalization, diuretics are given at higher dose and for a longer time during the hospital stay while beta-blockers, digoxin, anti-aldosterone agents, ACEi and ARBs are given less frequently in the former than in the latter. These behaviors will have relevant impact on prognosis during the chronic phase of disease.

Chronic HF and CKD

Renal impairment in patients with chronic HF is recognized as an independent risk factor for morbidity and mortality [5, 6, 36, 37, 55, 56]. Data from the SOLVD trial quantified specific clinical predictors of reduction in renal function in patients with chronic HF who were prescribed ACEi therapy [57]. Enalapril use caused a 33% increase in the risk of decreased renal function in these patients. Diuretic use and advanced age significantly increased this risk. Diabetes was associated with an increased risk of renal impairment in all patients with chronic HF, but this risk was reduced in the enalapril group compared with the placebo group. Interestingly, beta-blocker therapy and higher LV ejection fraction were renoprotective in all patients regardless of therapy (enalapril or placebo). Ahmed *et al.* [58] recently demonstrated that discharge prescription of ACEi/ARB was associated with a modest but significant reduction in all-cause mortality in older patients with systolic HF with CKD, including those with more advanced renal impairment, confirming that the

well-known decrease in renal function produced by ACEi administration, when limited to 20-30% of the eGFR value at baseline, has not detrimental effects on the long-term prognosis also in patients with CKD.

Despite the greater risk of mortality in patients with chronic HF and CKD, evidence has suggested that guideline-recommended therapies for HF are less likely to be provided to patients with comorbid chronic HF and CKD [57, 59-61]. In our experience cited above [49], we observed that patients who died were taking during follow-up less frequently diuretics and beta-blockers than those who survived, indicating possible history of intolerance, specific contraindications or evidence of side effects. Furthermore, we also documented that, among patients treated with beta-blockers during the period of observation, those who died were receiving a significantly lower dose of carvedilol than patients who survived. Several data consistently indicated the lack of treatment with beta-blockers or of reaching their target doses as a clinical marker of severity of cardiac disease related to poorer clinical outcomes in patients with chronic HF [62-66]. Even ACEi/ARB were less frequently given to our patients who died during 1-year follow up, mirroring a common practice attributable to lack of evidence of benefit and concern for potential harmful effects [67-69]. However, this medical behavior did not influence the outcome of our patients when adjusted for the other predictors. This result is reasonable in light of the results of several studies indicating the existence of a link between the worse clinical conditions at the time of hospitalization associated with older age [52, 53, 70] and the adverse outcome in our patients with severe CKD and acute HF. In this situation, the protective renal and cardiac effect of ACEi/ARB might play a less important role on outcome than that documented in patients with stable chronic HF without severe CKD [71], so that a reduction of the dose of ACEi may be taken into account, considering the results of Pita-Fernández *et al.* [72] who showed in elderly HF patients with CKD an improvement in anaemia and kidney function, and an increased survival rate.

Conclusions

Most patients with CKD have LVSD. This mirrors the influence of parenchymal CKD, renal artery disease, renal congestion and hypo-perfusion, neuroendocrine stimulation and the effects of pharmacological treatments. CKD negatively influences clinical outcomes both in primary and secondary prevention, in particular when HF syndrome develops. In the setting of asymptomatic patients with LVSD, the most important objective should be fight LV concentric remodeling/hypertrophy using ACEi/ARB, calcium antagonists and anti-aldosterone agents, the three classes of drugs with proved effects on the LV mass growth. Once the cardiac disease progresses towards HF, preventing CKD, discontinuing its progression and/or reversing CKD have to be the primary targets for the clinical management of these patients.

Riassunto

Una stretta relazione tra la funzione cardiaca e quella renale è presente in tutte le fasi evolutive delle cardiopatie e delle nefropatie, da quelle iniziali asintomatiche a quelle avanzate che culminano nello scompenso cardiaco conclamato e nell'insufficienza renale terminale, rispettivamente. La presenza di una alterazione, anche lieve, della funzione di un apparato condiziona la prognosi e la terapia della patologia conclamata dell'altro apparato. Il riconoscimento precoce delle anomalie della funzione cardiaca e renale è pertanto di notevole rilevanza clinica.

Parole chiave: scompenso cardiaco, disfunzione ventricolare sinistra, insufficienza renale, proteinuria, filtrato glomerulare

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