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 disease, 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...
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 patients 

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 consequent 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 word), 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 midterm 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-natriemia, 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 co-morbid 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 take 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.
Ventricular Dysfunction in Chronic Renal Disease

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 e nello scompenso renale terminale, rispettivamente. La presenza di una alterazione, anche lieve, della funzione di un apparato condiziona la prognosi e la terapia della patologia condizionata dall'altro apparato. Il riconoscimento precoce delle anormalità della funzione cardiaca e renale è pertanto di notevole rilevanza clinica. Parole chiave: scompenso cardiaco, disfunzione ventricolare sinistra, insufficienza renale, proteinuria, filtrato glomerulare

References

1. The role of the kidney in heart failure. Metra M, Cotter G, Gheorghiade M, Dei Cas L, Voors AA. Eur Heart J 2012; 17: 2135-2147.
2. Chronic Kidney Disease Prognosis Consortium. Association of estimated glomerular fliter rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet 2010; 375: 2073-81.
3. Tonelli M, Munter P, Lloyd A, et al. Using proteinuria and estimated glomerular filtration rate to classify risk in patients with chronic kidney disease: a cohort study. Ann Intern Med 2011; 154: 12-21.
4. Sarnak MJ. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation 2003; 108: 2154-69.
5. Dries DL, Exner DV, Domanski MJ, Greenberg B, Stevenson LW. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. J Am Coll Cardiol 2000; 35: 681-689.
6. Hillegaart H, Nitsch D, Pfeifer MA, et al. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. Circulation 2006; 113: 671-678.
7. de Haas RJ, Urso R, Laroche C, Damman K, Dahlström U, Tavazzi L, Maggioni AP, Voors AA. Morbidities in patients with heart failure: an analysis of the European Heart Failure Pilot Survey. Eur J Heart Fail 2014; 16: 103-111.
8. From AM, Leibson CL, Bursi F, et al. Diabetes in heart failure: prevalence and impact on outcome in the population. Am J Med 2006; 119: 591-599.
9. Paolietti E, Bellino D, Cassottana P, Rolla D, Cannella G. Left ventricular hypertrophy in nondiabetic predialysis CKD. Am J Kidney Dis 2006; 46: 320-327.
10. Foley RN, Parfrey PS, Harnett JD, Kent GM, Martin CJ, Murray DC, Barre PE. Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. Kidney Int 1995; 47: 186-192.
11. Levin A. Clinical epidemiology of cardiovascular disease in chronic kidney disease prior to dialysis. Seminars in diaylsis 2003; 2: 101-105.
12. Middleton RJ, Parfrey PS, Foley RN. Left ventricular hypertrophy in the renal patients. J Am Soc Nephrol 2001; 12: 1079-1084.
13. Paolietti E, Cassottana P, Bellino D, Specchia C, Messa P, Cannella G. Left ventricular geometry and adverse cardiovascular events in chronic hemodialysis patients on prolonged therapy with ACE inhibitors. Am J Kidney Dis 2002; 40: 728-736.
mortality in patients with type 2 diabetes mellitus. *Am J Cardiol* 2014; 113: 1409-1414.

31. Borlaug BA, Lam CS, Roger VL, Rodeheffer RJ, Redfiels MM. Contractility and ventricular systolic stiffening in hypertensive heart disease insights into the pathogenesis of heart failure with preserved ejection fraction. *J Am Coll Cardiol* 2009; 54: 410-418.

32. Mall G, Rambausek M, Neumeister A, Kollmar S, Vetterlein F, Ritz E. Myocardial interstitial fibrosis in experimental uremia—implications for cardiac compliance. *Kidney Int* 1988; 33: 804-811.

33. Amano K, West G, Zimmer G, Greiz N, Ritz E, Mall G. Reduced capillary density in the myocardium of uremic rats—a stereological study. *Kidney Int* 1992; 42: 1079-1085.

34. Amano K, Kronenberg G, Gehlen F, Wessels S, Orth S, Münster K, et al. Cardiac remodelling in experimental renal failure—an immunohistochemical study. *Nephrol Dial Transplant* 1998; 13: 1958-1966.

35. Schwartz K, Chassagne C, Boheler KR. The molecular biology of heart failure. *J Am Coll Cardiol* 1993; 22: 30-33.

36. Owman TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Secular trends in renal dysfunction and outcomes in hospitalized heart failure patients. *J Card Fail* 2006 May; 12: 257-262.

37. McAlister FA, Ezekowitz J, Tonelli M, Armstrong PW. Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. *Circulation* 2004; 109: 1004-1009.

38. Nieminen MS, Bohm M, Cowie MR, Drexler H, Filipatos GS, Iodice G, Hasin Y, Lopez-Sendon J, Münster K, Metra M, Magni AP, Tavazzi L, on behalf of Italian Acute Heart Failure Survey. Clinical features, in-hospital and 1-year mortality of patients with acute heart failure and severe renal dysfunction. Data from the Italian Registry IN-HF Outcome. *Intern J Cardiol* 2014; 172: e96-97.

39. Oliva F, Mortara A, Cacciagiu G, Chiniaglia A, Tarantini L, Metra M, Magni AP, Tavazzi L, on behalf of Italian Acute Heart Failure Survey. Clinical features, in-hospital and 1-year mortality of patients with acute heart failure and severe renal dysfunction. Data from the Italian Registry IN-HF Outcome. *Eur J Heart Fail* 2012; 14: 1208-1217.

40. Heywood JT, Fonarow GC, Costanzo MR, Mathur VS, Wigneswaran JR, Wynne J, ADHERE Scientific Advisory Committee and Investigators. High prevalence of renal dysfunction and its impact on outcome in 118,465 patients hospitalized with acute decompensated heart failure: a report from the ADHERE database. *J Card Fail* 2007; 13: 422-430.

41. Fonarow GC, Abraham WT, Albert NM, et al; OPTIMIZE-HF Investigators and Hospitals. Influence of a performance-improvement initiative on quality of care for patients hospitalized with heart failure: results of the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF). *Arch Intern Med* 2007; 167: 1493-1502.

42. Fonarow GC, Abraham WT, Albert NM, et al; OPTIMIZE-HF Investigators and Hospitals. Factors identified as precipitating hospital admissions for heart failure and clinical outcomes: findings from OPTIMIZE-HF. *Arch Intern Med* 2008; 168: 847-854.

43. Tarantini L, Cioffi G, Gonzini L, Oliva F, Lucci D, Di Tano G, Magni AP, Tavazzi L; Italian Acute Heart Failure Survey. Evolution of renal function during and after an episode of cardiac decompensation: results from the Italian survey on acute heart failure. *J Cardiovasc Med* 2010; 11: 232-243.

44. Bibbins-Domingo K, Lin F, Vittinghoff E, Barrett-Conner E, Grady D, Shlipak MG. Renal insufficiency as an independent predictor of mortality among women with heart failure. *J Am Coll Cardiol* 2004; 44: 1593-1600.

45. Ezekowitz J, McAlister FA, Humphries KH, Norris CM, Tonelli M, Ghali WA, Kudin ML; APPROACH Investigators. The association among renal insufficiency, pharmacotherapy, and outcomes in patients with heart failure and coronary artery disease. *J Am Coll Cardiol* 2004; 44: 1587-1592.

46. Cioffi G, Tarantini L, Pulignano G, Del Sindaco D, De Feo S, Opasich C, Di Lenarda A, Stefenealli C, Burlanello F. Prevalence, predictors and prognostic value of acute impairment in renal function during intensive unloading therapy in a community population hospitalized for decompensated heart failure. *J Cardiovasc Med* 2007; 8: 419-427.

47. Hillege HL, Girbes AR, de Kam PJ, Boomsma F, de Zeeuw D, Charlesworth A, Hampton JR, van Veldhuisen DJ. Renal function, neurohormonal activation, and survival in patients with chronic heart failure. *Circulation* 2000; 102: 203-210.

48. Saltzman HE, Sharma K, Mather PJ, Rubin S, Adams S, Whellan DJ. Renal dysfunction in heart failure patients: what is the evidence? *Heart Fail Rev* 2007; 12: 37-47.

49. Cioffi G, Mortara A, Di Lenarda A, Oliva F, Lucci D, Senni M, Cacciagiu G, Cinaglia A, Tarantini L, Metra M, Magni AP, Tavazzi L, on behalf of Italian Acute Heart Failure Survey. Clinical features, in-hospital and 1-year mortality of patients with acute heart failure and severe renal dysfunction. Data from the Italian Registry IN-HF Outcome. *Eur J Heart Fail* 2014; 16: 1056-1063.

50. Oxman TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Secular trends in renal dysfunction and outcomes in hospitalized heart failure patients. *J Card Fail* 2006 May; 12: 257-262.

51. McAlister FA, Ezekowitz J, Tonelli M, Armstrong PW. Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. *Circulation* 2004; 109: 1004-1009.

52. Nieminen MS, Bohm M, Cowie MR, Drexler H, Filipatos GS, Iodice G, Hasin Y, Lopez-Sendon J, Münster K, Metra M, Magni AP, Tavazzi L, on behalf of Italian Acute Heart Failure Survey. Evolution of renal function during and after an episode of cardiac decompensation: results from the Italian survey on acute heart failure. *J Cardiovasc Med* 2010; 11: 232-243.

53. Bibbins-Domingo K, Lin F, Vittinghoff E, Barrett-Conner E, Grady D, Shlipak MG. Renal insufficiency as an independent predictor of mortality among women with heart failure. *J Am Coll Cardiol* 2004; 44: 1593-1600.

54. Ezekowitz J, McAlister FA, Humphries KH, Norris CM, Tonelli M, Ghali WA, Kudin ML; APPROACH Investigators. The association among renal insufficiency, pharmacotherapy, and outcomes in patients with heart failure and coronary artery disease. *J Am Coll Cardiol* 2004; 44: 1587-1592.

55. Knight EL, Glynn RJ, McIntyre KM, Mogun H, Avorn J. Mortality in patients with type 2 diabetes mellitus. *Am J Cardiol* 2014; 113: 1409-1414.
59. Lahoz C, Mostaza JM, Mantilla MT, Taboada M, Tranche S, Lopez-Rodriguez I, Monteiro B, Soler B, Sanchez-Zamorano MA, Martin-Jadraque R. Achievement of therapeutic goals and utilization of evidence-based cardiovascular therapies in coronary heart disease patients with chronic kidney disease. *Am J Cardiol* 2008; 101: 1098-1102.

60. Patel UD, Hernandez AF, Liang L, Peterson ED, LaBresh KA, Yancy CW, Albert NM, Ellrodt G, Fonarow GC. Quality of care and outcomes among patients with heart failure and chronic kidney disease: a Get With the Guidelines-Heart Failure Program study. *Am Heart J* 2008; 156: 674-681.

61. Berger AK, Duval S, Manske C, Vazquez G, Barber C, Miller L, Luepker RV. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients with congestive heart failure and chronic kidney disease. *Am Heart J* 2007; 153: 1064-1073.

62. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999; 353: 2001-2007.

63. The Cardiac Insufficiency Bisoprolol Study II (CIBIS II): a randomized trial. CIBIS II investigators and committees. *Lancet* 1999; 353: 9-13.

64. Bristow MR, Gilbert EM, Abraham WT, et al. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. MOCHA Investigators. *Circulation* 1996; 94: 2807-2816.

65. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. *N Engl J Med* 1996; 334: 1349-1355.

66. Zageck C, Haumstetter A, Krager C, et al. Impact of beta-blocker treatment on the prognostic value of currently used risk predictors in congestive heart failure. *J Am Coll Cardiol* 2002; 39: 1615-1622.

67. Bart BA, Gattis WA, Diem SJ, O’Connor CM. Reasons for underuse of angiotensin-converting enzyme inhibitors in patients with heart failure and left ventricular dysfunction. *Am J Cardiol* 1997; 79: 1118-1120.

68. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? *Arch Intern Med* 2000; 160: 685-693.

69. Ahmed A. Use of angiotensin-converting enzyme inhibitors in patients with heart failure and renal insufficiency: how concerned should we be by the rise in serum creatinine? *J Am Geriatr Soc* 2002; 50: 1297-1300.

70. Spinar J, Parenica J, Vitovec J, et al. Baseline characteristics and hospital mortality in the Acute Heart Failure Database (AHEAD) Main registry. *Crit Care* 2011; 15: R291.

71. Bowling CB, Sanders PW, Allman RM, et al. Effects of enalapril in systolic heart failure patients with and without chronic kidney disease: Insights from the SOLVD Treatment trial. *Int J Cardiol* 2013; 167: 151-156.

72. Pita-Fernández S, Chouciño-Fernández T, Juega-Puig J, Seoane-Pillado T, Lázaro-Calviño B, Péreza-Díaz S, Pedreira-Andrade JD, Gil-Guillén V. A randomized clinical trial to determine the effect of angiotensin inhibitors reduction on creatinine clearance and haemoglobin in heart failure patients with chronic kidney disease and anaemia. *Int J Clin Pract* 2014 Jul 16. doi: 10.1111/iifp.12475.