PROFESSIONE NEFROLOGO

Cardionephrology: past, present and future

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Abstract

In 1987, the first Kidney-Heart meeting was held in Assisi, Italy and in 1991 the term Cardionephrology was coined in medical practice. Since then, nephrologists and cardiologists realized the utility of a tight cooperation among them and organized an agenda of scientific meetings which take place every two years within European countries. The cooperation was strengthened by daily observation which shows renal replacement therapy had solved many problems but imposed or added new disorders to cardiovascular system. Soon, the nephrologists learned that hemodialyisis techniques had not only blood detoxification effect but also cardiovascular consequences. Therefore, the nephrologists started to adopt cardiological tools and apply them to renal patients. The cardiologists realized that in some aspects kidney patients are different from non-renal cardiological patients and have to be treated differently.

In Assisi Cardionephrology meetings a clear message was launched: the necessity to bring nephrologists and cardiologists together with the potential benefit of learning from others experiences and transferring the outcome for the benefit of our patients.

As result, many foundations and journals have been emerged on this topic.

Is there a future for Cardionephrolgy? The answer is yes, with a unique limitation: to continue the spirit of Assisi, following the culture of cooperation and relying on RCTs hypothesis.

Key words: cardionephrology, link, renal-cardio disease

The start-up

Rumor says that it was a winner idea to coin and introduce the term *Cardionephrology* in the Assisi meeting of 1991. Successor to regular congresses that started in 1987 and ended in 2013 every other year, Assisi meetings focused on cardiovascular topics of common interest for nephrologists and cardiologists. Apart from scientific presentations and educational sessions concentrating on up-to-date clinical problems, the conferences stimulated and promoted a cooperation between cardiologists and nephrologists.

When the first meeting took place in 1987, little knowledge was available on the cardiovascular risk associated to chronic renal insufficiency. Some concepts and paradigms about the interrelationship between heart and kidney were published by Lindner and Charra [1] in 1974, by Vincenti et al. [2] in 1980, by Rostand et al. [3] in 1982, by Degoulet et al. [4] in 1982 and by Ikram [5] in 1983.

The 1970ies had been a period of finding and defining the most practicable and most efficient blood purification methods: CAPD, hemofiltration and hemodiafiltration extended therapeutic choices. However, argument pro and contra a specific method nearly exclusively based on blood purification properties grew up more and more. Technological progress such as control of ultrafiltration and bicarbonate buffer increased the tolerance of hemodialysis(HD). Consequently the method could be applied to a much larger group of end-stage renal-disease (ESRD) patients which in a still ongoing process have become not only older but also burdened by cardiovascular co-morbidity.

Simultaneously, new diagnostic techniques such echocardiography not only empowered cardiologists to enlarged their diagnostic and therapeutic spectrum, it also stimulated nephrologists due to their interest in arterial hypertension. Therefore, it is no surprise that echocardiographic follow-up of ESRD patients was established in Newfoundland (Canada) by Parfrey [6], and the main topic of the first congresses of Giessen [7] and Assisi [8] were on echocardiographic findings in ESRD patients. The experience that hemodialysis methods had not only blood detoxification properties but also distinct acute and chronic cardiovascular consequences per se in patients with or without pre-existing cardiovascular disease, further stimulated the notion that nephrologists and cardiologists have to cooperate. The combined knowledge was concentrated in the eponymous *Cardionephrology* in the third Assisi meeting (1991).

When an idea becomes reality

The evolving concept during the international conferences was to bring cardiologists and nephrologists together with the potential advantage of learning from each other, and collaborating for the benefit of the patients. A tight collaboration was the first and principal suggestion of Assisi Cardionephrology meetings and the creation of common team of cardiologists and nephrologists was proposed.. To day in some Italian hospitals this encouragement has become a reality, though under different initials.

Nephrologists started to adopt cardiological methods and apply them on HD patients. Cardiologists learned that renal patients differ and that proven therapeutic strategies evidenced in non-renal patients could not transferred to patients with renal failure. Nephrologists more and more became aware the renal replacement therapy has solved many problems, but imposed or added new derangements to the cardiovascular system. They learned that myocardial infarction, sudden cardiac arrest and congestive heart failure are the cause of mortality in more than half of patients with chronic disease after correction for age, race and diabetes.

Since the first Assisi meetings, the increased prevalence of cardiovascular risk starting at early stages of renal disease was reported and debated.. Thus, meeting by meeting, strategies were presented for developing comprehensive and reliable methods for early identification of cardiac disorders, for implementation of therapeutic procedures able to attenuate, halt or reverse cardiovascular disease and eventually to prolong survival [9].

A second step focused on the identification of the link between early chronic renal disease (CKD) and cardiovascular derangements, later confirmed by epidemiologic studies. Since the first Assisi meeting the notion has been proposed that early stages of CKD might not only be associated with increased prevalence and incidence of chronic cardiovascular disease(CVD), but also causally related..

Thirdly, the majority of patients with CKD die before progressing to renal replacement treatment. Dialysis patients seem to be <survivors> in the natural history of renal disease.

A large longitudinal follow-up of patients with early CKD followed for five years, found that 31% progressed to ESRD, 24% died before the start of dialysis: cardiovascular diseases may have accounted for the majority of death [10]. Current guidelines acknowledge that CKD patients have a high risk of CVD. This is in line with the continuous task of *Cardionephrology* and of 25-year Assisi conferences, which provided a robust message of kidney and heart protection as the core of its educational activity.

The accumulation of a vast amount of knowledge in C*ardionephrology* in the 14 Assisi conferences underlines the statement that there is no nephropathy, including inherited congenital illness such as polycystic kidney disease or Fabry disease, without cardiovascular involvement. Therefore C*ardionephrology* probably represents the core part of nephrology.

In Assisi we did the logical thing: to concentrate the already existing and incoming knowledge into a common meeting of specialists. In addition, we may have stimulated further research in this area.

Search in Pubmed for the term "Cardiorenal" indicates that only 63 papers were on this topic before 1990, increasing to 141 for the period 1991-2000 and further mounting to 373 since 2001 and to reach 978 in 2010.. In the same intervals the number of papers on "hepatorenal" relations remained the same, so the increase is clearly not caused only by the increasing overall number of medicine papers.

In addition to traditional cardiorenal topics, Assisi meeting provided an overview of the burden of emerging disorders linking heart to kidney, and of evidence for the inflammatory nature of cardiorenal diseases. New theories were controversially discussed. The emerging topic presented in Assisi included the heart in glomerulonephritis, cardiorenal disease in the women, ischemic renal disease and cardiac involvement, coronary surgery in renal patient, genetic mechanisms of systemic hypertension, dipper and non-dipper phenomenon in hypertension, proteinuria and cardiac risk, hyperuricemia and cardiorenal risk, cardiovascular disease and adequacy of dialysis, new aspects of arrhythmias in dialysis, Klotho and inflammation in cardiorenal patients, obesity and CKD, controversies on hypervolemic dialysis patients, kidney and heart failure, cardiac derangement after renal transplantation, therapies to ameliorate anemia and to prevent cardiovascular calcification, bone-kidney-heart axis.

Cardiological procedures in ameliorating cardionephrology diagnosis

Since the first Assisi meeting left ventricular hypertrophy assessed by echocardiography was one of the main topics [11].However, prevalence and natural course were probably overestimated due to the poor quality of echo results compared to the current gold standard of cardiac NMR. This early error was later understood and corrected, according to the philosopher Karl Popper who stated that mistake is a right step to approach the truth as a consequence of the renowned rule of "trial and error" in scientific procedure.

The importance of achieving an almost normal hematocrit in ESRD patients was overestimated and the consequences of erythropoietin therapy in getting such a goal are probably overlooked, which, at its period (before large randomized studies were published) was in line with the discussions in general nephrology.

Assisi meetings probably had manifested formal consequences. The new SIN study group of "*Cardionefrologia*" and the European scientific associations such as EURECA-m(European Renal Cardiovascular Medicine) and ECNA (European CardioNephrology Association) are

eloquent confirms. The recent journal named "Cardiorenal Medicine" published by Karger Basel is another sign of spreading interest for the kidney-heart connection.

At this point some questions are unavoidable: what has been the influence of *cardionephrology* on Italian and other European nephrologists and cardiologists beyond those formal progresses?

Was there an impact (if any) on every day clinical practice in renal patients?

Were cardiologists effectively involved in the domain of *Cardionephrology*?

In Germany the concept to bring together the two groups of specialists failed mainly due to the indifference of cardiologists.. After a slow beginning the real impact on Italian nephrologists became stronger when drugs entered into the market to treat some common derangement such as anemia and cardiovascular calcification, which were important topics in Assisi. However, being a scientific and educational congress, Assisi conferences tried to promote independent and critical opinion.

Is there a future for cardionephrology? The answer is a yes but with some limitations. Of course, scientific studies, detection of new diagnostic procedure and new therapeutic concepts in this area will continue. However, serious doubts of the clinical sequelae of such studies are appropriate.

What we can learn from the history of erythropoietin trials is the notion that at present only large independent prospective randomized trials (RCTs) can give definite answers and thereby actually help patients. In this area there is no hard evidence for most of our practical actions in treating kidney patients. In the field of *Cardionephrology* this concerns nearly all pharmacotherapy. Can current therapy of cardiac failure be transferred to ESRD patients? What is the best strategy for treating coronary heart disease in those patients? Have phosphate binders any proven therapeutic value at all? Has PTH a diagnostic value and cinacalcet a prognostic impact? Why are nephrologists disappointed on the results of EVOLVE study which evaluated the role of PTH on reducing cardiovascular events [12] (full text)? When we anticoagulate dialyisis patients will there be more benefit or harm [13]? Do new diagnostic tools like bioimpedence for assessing dry weight or lung sonography for measuring lung water, influence the outcome? Is there any hard evidence that a correction of pathological states increase survival? Is our current practice of dialysis with a "Procuste's" dialysis of fixed schedules and duration adequate for the recipients? In addition, is real the overdiagnosis of chronic kidney disease recently underlined on British Medical Journal [14]. How do we have to define hypertension in ESRD patients and how have we treat them?

A small selection of eventually unanswered questions, which not only concern the future of c*ardionephrology* but nephrology itself.. If nephrology will overcome the status of primarly being a discipline of almost unproven (by RCTs) hypotheses we recommend the culture of *cardionephrology*. Which culture? It is the culture of cooperation. The willingness of learning from a partner. What can we nephrologists learn from cardiologists? Well: we can learn from them what we require most: how to obtain evidence for therapeutic decisions. To rely on RCTs instead of trusting on associative studies. To accept a new drug only when a superior outcome for the patients has been largely proven. To build large network for conducting appropriate independent studies, to cooperate to practice the culture of *cardionephrology*. The spirit of Assisi.

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