




EDITORIAL COMMENT

Cardioneurology from the point of view of the cardiologist: no more agree to disagree—getting to ‘yes’ for every patient

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ABSTRACT

Whether one wants to or not, interactions between the heart and the kidneys exist and manifest nevertheless. Both from theoretical and clinical perspectives, it seems the need for a subspecialty of cardioneurology seems justified. Our editorial is a cardiologist perspective on the article by Diez and Ortiz published in *Clinical Kidney Journal* related to the ‘need for a cardioneurology subspecialty’. We analysed the historical similarities of the emergence of already ingrained clinical fields with the current needs in the cardioneurology sector. We motivated our approach based on novel cardiovascular diagnostic and therapeutic developments and significant pathophysiological differences from a cardiological perspective, accounting for the foundation of a novel sustainable medical field. One of the sensitive issues we also addressed was the operability and applicability of the principles. We answered with some examples from high-risk debatable contexts the question of where a cardioneurologist should be integrated. Clarifying the operability aspects would be a positive shift towards improving guidelines adherence in managing complex patients. In conclusion, we underline that the necessity of a cardioneurologist must be addressed from an operational and scientific perspective, with the ultimate goal of reducing mortality and complications in cardiorenal patients.

Keywords: cardiac diseases, cardioneurology, chronic kidney disease, subspecialty

Whether one wants to or not, interactions between the heart and kidneys exist and manifest nevertheless; both physiological and pathological; likewise the (hopefully positive) intersections between cardiologist and nephrologist. Both from theoretical (pathophysiological) and clinical (pathological) perspectives, it seems that the need for a subspecialty (or a ‘superspecialty’) in cardioneurology is justified.

We read with great interest the article by Diez and Ortiz published in *Clinical Kidney Journal* related to the ‘need for a cardioneurology subspecialty’ [1]. It reminded us a lot of another brilliant editorial published 4 years ago that was ‘a call to action to stimulate universities, medical schools, and teaching hospitals to create a core curriculum for cardiorenal medicine, as has been done for critical care nephrology, cardiac critical care, and other

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disciplines that bridge the knowledge and skills between fields of cardiology and nephrology' [2].

Looking closely at the history of the emergence of clinical fields such as cardiology (17th century) [3], nephrology (1960) [4] and gastroenterology (1980) [5] that were initially incorporated in internal medicine training, one may detect similarities with the current situation. Some patterns seem always to be present when the moment comes for consolidating new medical branches, including refractory voices and opinions. Cardiology, nephrology and gastroenterology emerged from internal medicine in appropriate moments in time when particular guidelines and technical developments of specific diagnostic and therapeutic procedures allowed them to self-delimit as distinct medical branches (e.g. assessment of blood circulation and cardiac anatomy and pathology, auscultation, cardiac catheterization [3], biopsy needle, haemodialysis, microscopy, organ transplantation [4] or the introduction of endoscopy [5]).

Furthermore, the differentiation of new clinical fields occurred when they were most needed; more precisely, when scientific research revealed that hospital admissions to standard clinical specialties were inappropriate and overwhelming, when total assessment was necessary for optimum patient management and when there was a lack of education or ignorance within medical staff on the principles of care of a specific medical field [6].

Considering the current context of the intersection between cardiology and nephrology, one can see that all the patterns mentioned above are currently identified in the cardiorenal field as well. Modern diagnostic and therapeutic methods have been developed that are friendly and safe for cardiorenal patients, such as low-contrast percutaneous coronary interventions [7]; drug-eluting stents requiring a short course of dual antiplatelet therapy, which may be ideal for patients with end-stage kidney disease (ESKD) [8]; or advanced heart failure therapies such as left ventricular assist device implantation [9]. These modern methods constitute an arsenal for a safe and responsible fight against cardiorenal diseases, accounting for the foundation of a novel sustainable medical field.

The article by Diez and Ortiz highlighted, from the nephrologist perspective, that in CKD 'cardiovascular aspects do not receive the attention that corresponds to their burden of disease'. Moreover, few papers address the reversed context of the CKD risk in primarily cardiovascular patients and most acute heart failure studies have limited their investigation of short-term complications such as acute kidney injury (AKI) [10, 11]. Three of four studies assessing the risk of ESKD development in cardiovascular patients have included only selected populations (comorbidities like diabetes mellitus or CKD) in their investigation, leaving the general population unexplored [12–14].

The cardiologist perspective is at least equally worth considering, as cardiovascular diseases seem to be linked to an increased risk of kidney failure as well [15, 16]. More precisely, heart failure, atrial fibrillation, coronary heart disease and stroke are associated with the progression of CKD and the development of ESKD, heart failure being the most robust predictor [15]. It is essential to highlight that current evidence of the impact of cardiovascular disease on the long-term risk of CKD progression is even more neglected, both in the scientific literature and in clinical practice. All these inherently lead to 'unsatisfactory, unsafe, and ignorant patient management' in the nephrology and cardiology departments, interspecialty disagreements being the rule rather than the exception; one could easily see this neglect in the 21st century found in unexpectedly

and unjustifiably high rates of mortality and cardiovascular events in advanced kidney patients [17].

Interspecialists disagreements are also born of the conflicting approaches in pathophysiology, risk factors, diagnostic methods and treatment responses in overlapping cardiovascular and renal disorders. On the one hand, Diez and Ortiz succinctly and accurately illustrate the main pathophysiological mechanisms of systemic macro- and microvascular damage in CKD and other uraemic factors that may ultimately lead to cardiac impairment. On the other hand, the cardiologist's perspective highlights how higher levels of renin-angiotensin-aldosterone system activity during heart failure may lead to inflammation, oxidative stress and endothelial dysfunction, with damaging effects on the kidney [18]. Moreover, several standard medications used in cardiovascular diseases, such as loop diuretics or contrast agents, are nephrotoxic [19]. Regarding the fear of treatment risks and technical complications, some cardiologists may treat renal patients less vigorously than non-renal patients (e.g. 'therapeutic nihilism') [20].

To successfully manage a cardiorenal patient in a comprehensive, unified manner, a cardiorenal specialist should master both disease perspectives; e.g. 'diastolic malfunction contributes to the risk of pulmonary edema, on the one hand, and to the risk of hypotension during volume subtraction by ultrafiltration, on the other hand' [20].

The current emerging evidence, along with the existing knowledge gaps, point in the same direction. As anticipated, a cardioneurology subspecialty emerged as a matter of course. Beyond this statement lies a body of evidence comprising clinical protocols [21], growing evidence-based literature [22] and medical books [23] exclusively addressing this specialty niche. However, all the evidence acquired to date is unsystematized and unorganized and therefore significant knowledge gaps and a lack of studies and recommendations on the management of such a narrow patient sector are evident.

It may be that only through the eyes of a dedicated physician will sufficient clinical experience be gained in this niche specialty to systematize and organize knowledge and produce the most authentic and reliable management guidelines. Behind this approach is the necessity to reduce mortality and complications (in cardiac patients with renal dysfunction and in renal patients with cardiac complications, which often seem to be one and the same).

A cardioneurology specialty will provide the opportunity to solve interspecialty disagreements by going beyond the 'agree to disagree' concept' to a uniform, unique and accurate vision of disease management. Cardioneurologists will also have the advantage of better knowledge of the patient's history and closely monitoring the disease course compared with the context of distinct cardiology and nephrology specialists who do not have access to the complete patient picture.

One of the sensitive issues we want to address is not the scientific basis of this new discipline ('initially sustained by passionate specialists interested in the cross-fertilization between the two fields, cardiorenal medicine is now a discipline whose time has come' [2]), but the 'operationality and applicability' of the principles as mentioned earlier. That is, if we were to ask who would be the one to deal with cardiorenal pathology, we would argue that a cardiologist with training in nephrology should. In our opinion, where the cardiology guidelines speak of refraining from referring a renal patient to percutaneous coronary interventions or to receiving maximum cardiological medication in acute coronary syndrome (ACS) (the so-called therapeutic nihilism), clear evidence-based indications must

endorse the necessity of a written opinion of a cardioneurologist. We believe that this would be a positive shift towards improving guidelines adherence in managing complex patients and (probably) a reduction of the significant clinical endpoints.

Another provocative question is 'do we really need a subspecialty in cardioneurology or is it enough to operationalize a nephro-heart team on the Heart Team model?' [24]. The answer is not straightforward, as advantages and disadvantages exist in both cases. There is some evidence of the effectiveness of a cardioneurology multidisciplinary team (MDT). MDT meetings have been reported to play an essential role in managing cardiorenal syndrome, leading to improved care outcomes through evidence-based practice and better utilization of healthcare resources [25–27]. Although consensus decisions by the MDT are probably the (present) best possible scenario, real-life clinical settings may face various challenges in different interpretations of scientific data or clinical guidelines, professional conflicts, toxic interpersonal relationships or personal motivations [28]. These differences may lead to disagreement within a team, which in turn may negatively impact patients' management.

A multiperspective, team-based interview study examined the cooperation between cardiology and nephrology teams for treating patients with advanced heart failure. Despite a shared narrative of common purpose, this study reported that care activities involved communal tension through 'asynchronous clinical interpretations, geographically distributed specialist care, fragmented forms of communication, and uncertainty due to clinical complexity' [29]. When evaluating whether treatments recommended by a Heart Team differ from those recommended by an original treating interventional cardiologist, 30% of cases of divergent opinions (Heart Team versus interventional cardiologist) involved a greater level of disagreements within the Heart Team as well [30].

Additionally, the MDT's general opinion is not yet clearly defined in terms of applicability, reproducibility, decision-making processes, shared metrics and internal and external validity [28, 31]. Substantial disagreement was reported between cardiologists within various hospitals when asked whether a Heart Team existed in their hospital [32]. The results of this survey highlight the need for further refinement of the definition of a Heart Team and measures of successful implementation.

These findings lead us to opine that a subspecialty in cardioneurology could help overcome the barriers specific to MDT implementation. However, as the common goal is the patients' favorable outcomes, further prospective and randomized trials are needed to draw firm conclusions. Furthermore, following the history of implementing the Heart Team into the guidelines, with a dedicated focus on this very issue, one could easily introduce in the cardiovascular guidelines a recommendation for requesting the opinion of a cardioneurologist.

To the question of where a cardioneurologist should work or be integrated, we would like to answer with some examples from opposed contexts, which have in common the significant number of complex patients involved.

The first context is that of ACS management. There are two categories of patients who make up a significant percentage of those with ACS. One is represented by patients with ACS in whom routine protocols discover a renal dysfunction and another represented by known CKD patients who manifest an acute coronary event. These patients can only be treated in the context of the same circuits: interventional cardiology room, coronary care units and then a cardiology ward, and possibly a cardiovascular rehabilitation department. All these institutions

cannot be easily replaced, and it is pretty challenging to introduce a cardiorenal unit inside their operative flow. Instead, a cardiorenal expert attached to the entire department would be very appropriate here to focus specifically on the management and supervision of renal dysfunction, with all that this entails: medication adjustment, treatment protocols, dialysis decisions and specific prevention of AKI. We believe that by doing so, one can rapidly see positive changes in cardiovascular outcomes.

A second aspect is the primary prevention of cardiovascular events in two (large) categories of patients: advanced renal patients who have not had (yet) a cardiovascular event and asymptomatic individuals with multiple cardiovascular risk factors and mild renal dysfunction. The solid evidence so far shows that the presence of (even mild) renal dysfunction significantly increases the risk of major cardiovascular events in the two categories. Again, we believe that a dedicated cardioneurologist managing these two groups of patients could significantly benefit patient mortality and major adverse cardiovascular events.

The following two contexts are cited as a source of a lack of consensus between cardiologists and nephrologists. The clinical aspect causing interspecialty tension is stopping renin-angiotensin-aldosterone system inhibitors (RAASi) in heart failure patients with CKD; most often these drugs are withdrawn for fear of hyperkalaemia, azotaemia or hypotension and thus the move is anticipatory. As shown by several studies [33–35], this management decision is consistently associated with worsened outcomes, as discontinuing RAASi in heart failure may generate acute haemodynamic deterioration and higher death rates [36, 37]. Several solutions have been proposed to solve the clinical dilemma of stopping RAASi. Strong evidence suggests that the use of potassium binders enables the safe continuation of RAASi therapy [38]. Moreover, evidence underlines that RAASi 'have come to be widely but wrongly seen as "nephrotoxic"' despite the absence of evidence of RAASi discontinuation benefits in preventing AKI [39].

Finally, the two specialties' communication limitations and divergent attitudes regarding a single condition (e.g. AKI and acute tubular injury) lead to unjustifiably high mortality rates. While the cardiologist is limited to repeated measurements of serum creatinine (which is an insensitive and unreliable biomarker since its concentration does not increase significantly until about half of the kidney function is lost) [40], the nephrologist uses a 'double-edged sword' (e.g. fluid overload) that in turn generates other cardiovascular complications [41]. While monitoring haemodynamic parameters, updating echocardiography parameters and adjusting cardiovascular medication, a dedicated cardioneurologist could easily explore the necessity of using novel biomarkers (e.g. kidney injury molecule-1, neutrophil gelatinase-associated lipocalin or interleukin-18), which could have significant importance for early diagnosis and clinical course [40, 42].

In conclusion, we underline that the need for a cardioneurologist must be addressed from two perspectives:

1. From the operational perspective, the practitioner's view or the organizational point of view (Where does a cardioneurologist work? Should patients be admitted in a dedicated cardiorenal sector or should a dedicated cardioneurologist be available in the current care settings? Who should be the focus of activity for a cardioneurologist: acute patients or chronic patients? What will the final curricula look like: expanded cardiology or a nephrologist with another competence in cardiology? Is the result of this subspecialty a two-

in-one physician or should we clearly say from the beginning that a cardioneurologist will take care of specific problems and not 'pure' cardiac pathology or 'pure' kidney pathology?)

- From the scientific perspective (What issues are not yet highlighted in the management of these patients? What studies are needed? Who will recommend the final decision: an MDT of cardiologists and nephrologists or a single cardioneurologist?).

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CONFLICT OF INTEREST STATEMENT

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