Kidney disease in cardiology

Charles A. Herzog

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Focusing on the convergence of cardiology and nephrology, this article marks the second year of NDT’s section on Kidney Diseases beyond Nephrology. The clinical themes highlighted by the articles chosen for review include risk stratification and diagnosis of ischemic heart disease in severe chronic kidney disease and end-stage renal disease patients, trials to reduce the risk of acute kidney injury (particularly contrast nephropathy) occurring with the invasive diagnosis and treatment of ischemic heart disease, and new data on the special clinical characteristics of dialysis patients with acute myocardial infarction. Finally, two clinical trials focusing on cardiovascular disease in severe kidney disease patients will be briefly highlighted.

Keywords: acute kidney injury; acute myocardial infarction; chronic kidney disease; dialysis; ischemic heart disease

Editorial Review

Kidney disease in cardiology

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Abstract

Focusing on the convergence of cardiology and nephrology, this article marks the second year of NDT’s section on Kidney Diseases beyond Nephrology. The clinical themes highlighted by the articles chosen for review include risk stratification and diagnosis of ischemic heart disease in severe chronic kidney disease and end-stage renal disease patients, trials to reduce the risk of acute kidney injury (particularly contrast nephropathy) occurring with the invasive diagnosis and treatment of ischemic heart disease, and new data on the special clinical characteristics of dialysis patients with acute myocardial infarction. Finally, two provocative clinical trials focusing on cardiovascular disease in severe CKD and ESRD patients will be briefly highlighted.

Risk stratification

Echocardiography plays a key role in the cardiac evaluation of ESRD patients, as evidenced by the US National Kidney Foundation Kidney Disease Outcomes Quality Initiative practice guidelines, recommending echocardiograms for all dialysis patients 1 to 3 months after initiation of renal replacement therapy and at 3 year intervals subsequently, irrespective of symptoms [1]. Recent works by Rakhit et al. [2] and Sharma et al. [3] refine our nuanced understanding of the role of echocardiography in risk stratification.

Rakhit et al. [2], of Brisbane, Australia, prospectively followed a cohort of 129 patients with severe CKD and normal dobutamine stress echocardiographic (DSE) findings (no evidence of ischemia or left-ventricular systolic dysfunction). Myocardial tissue characterization was performed using tissue Doppler imaging (a technique widely employed in current clinical practice) and integrated backscatter (not typically used clinically). Patients were followed for cardiac events and all-cause mortality over 2.4 years. Previous cardiac history and serum phosphate were the strongest demographic or clinical independent predictors of outcome. Diastolic tissue velocity, one of several markers of subclinical left-ventricular (LV) dysfunction, added incremental independent prognostic value when added to clinical parameters. Patients who were on dialysis at follow-up had a significant reduction in diastolic tissue velocity, a finding consistent with a greater burden of cardiomyopathy, while patients who were transplanted had an increase, suggesting that transplantation potentially reverses some of the cardiomyopathy, which progresses in dialysis patients. Also of interest, at initial screening, all 129 patients with ‘normal’ dobutamine stress echocardiograms showed some evidence of subclinical myocardial dysfunction.

Sharma et al. [3] prospectively analyzed preoperative echocardiographic and other clinical parameters 5.1 ± 2.2 months [mean ± standard deviation (SD)] before renal transplantation in 203 renal transplant recipients who

It is a brilliant fall in Minneapolis, but winter will again be upon us (and, hopefully, a new bridge raised to replace the one that failed catastrophically on 1 August 2007) by the time this review is published. Nearly a year has passed since the inauguration of Kidney Diseases beyond Nephrology; it is once again time to sift through the literature to highlight papers dealing with cardiac disease relevant to nephrologists and published in non-nephrology journals. Some themes previously addressed will be reprised (along with my apologies for not including the many worthy papers meriting discussion), as they figure prominently in recent publications. These include risk stratification and diagnosis of ischemic heart disease in severe chronic kidney disease (CKD) and end-stage renal disease (ESRD) patients, trials to reduce the risk of acute kidney injury (particularly contrast nephropathy) occurring with the invasive diagnosis and treatment of ischemic heart disease, and new data on the special clinical characteristics of dialysis patients with acute myocardial infarction (AMI). Finally,
received grafts in the United Kingdom in 1996–2001 for the prediction of all-cause mortality (follow-up 3.6 ± 1.9 years, mean ± SD). Some patients were deemed ineligible who might have been considered for transplantation in selected North American centers (e.g. LV ejection fraction <25%, body mass index >35 kg/m², severe peripheral vascular disease). Mean age of the cohort was 47 ± 12 years; 21% had diabetes and 93% were dialysis dependent. Only 20 ‘low-risk’ patients received no preoperative assessment for coronary artery disease (CAD), 45 patients (22%) underwent coronary angiography and 13 patients received coronary revascularization. Post-operative mortality at 28 days was 1.5%, and estimated Kaplan–Meier 5-year cardiovascular and all-cause mortality were 15% and 24%, respectively. (For comparison, the 5-year survival of first-time US transplant patients in 1999 was a qualitatively similar 80%, and mortality more than 1 year after transplantation has changed little over time [4].) Nine patients (4.4%) had myocardial infarction, with seven fatalities. In a multivariate model, independent predictors of mortality were age ≥ 50 years, echocardiographic measurements of LV end-systolic dimension ≥ 3.5 cm, maximal LV wall thickness ≥ 14 mm and presence of mitral annular calcification. Patients ≥ 50 years with two of the three additional prognostic variables had a 5-year mortality of 82%. These interesting data on preoperative risk stratification, which rely heavily on echocardiography, await confirmation from other investigators, particularly as other centers (including ours) may treat patients with higher diagnosed prevalence of obstructive CAD in transplant-eligible patients.

DSE plays a key role in the noninvasive diagnosis of CAD in ESRD patients [5]. Bergeron et al. [6] at the Mayo Clinic (Rochester, MN, USA) retrospectively analyzed the prognostic utility of DSE in 485 patients with severe CKD (245 with creatinine >3 mg/dL, 240 on dialysis). Mean age was 61 ± 12 years; diabetes was the primary cause of renal disease for 38% of patients and a comorbid condition for 49%, and only a third of the patients received subsequent renal transplants. This cohort was thus at much higher cardiovascular risk than the cohort in the study by Sharma et al. [3]. In all, 58% of patients had abnormal DSE, defined as inducible ischemia (40%) or fixed abnormality (indicative of previous infarct without inducible ischemia); 18% of patients (n = 85) were subcategorized for ‘extensive ischemia’ if >25% of LV segments had inducible ischemia. The estimated 3-year Kaplan–Meier survival was 70% for patients with normal DSE, 57% for patients with fixed defect without inducible ischemia, 52% for patients with non-extensive ischemia (≤25% of LV segments) and 48% for patients with extensive ischemia. The real clinical dichotomy (in my opinion) is therefore not the degree of inducible ischemia, but rather the presence of any defect (i.e. due to scar or obstructive CAD in a viable coronary artery vascular territory). This interpretation is also concordant with the meta-analysis by Rabbat et al. [7], who reported an equivalent adverse outcome for both fixed defects and inducible ischemia in ESRD patients. I suspect that arrhythmic death (related to peri-infarct border zone electrical instability in areas of myocardial scar) is the mechanism of adverse cardiovascular outcome in patients with fixed defects and no evidence for inducible ischemia.

An interesting sidebar to our discussion of cardiac screening for renal transplant candidates is provided by Hage et al. [8] who reviewed the University of Alabama (US) renal transplant database of 3698 patients evaluated for kidney transplantation in 2001–2004. Per institutional protocol, stress nuclear perfusion imaging was performed on a selected subset of 2207 higher risk patients, comprising 60% of the cohort (e.g. patients aged >50 years, with prior history of cardiovascular events, etc.). Surprisingly, 80% of the studies were normal, 14% had evidence for inducible ischemia and 5% had scar. The authors confirmed the importance of left-ventricular ejection fraction (LVEF) and its association with increased mortality; the adjusted hazard ratio of LVEF ≤40% was 1.9 (95% confidence interval 1.49–2.34). Concordant with earlier data cited, any perfusion abnormality was predictive of worse survival, but there was no difference between inducible ischemia and fixed defects. The most interesting part of the paper (and not emphasized by the authors) is the implicit under-detection of obstructive CAD by nuclear imaging, as a high-cardiac-risk subset of patients had only a 20% rate of abnormal studies, and only 7% of the entire cohort underwent coronary angiography versus 22% of patients in the study by Sharma et al. [3].

In a prior study by Sharma et al. [9] of 118 consecutive, un-selected, renal transplant candidates prospectively undergoing DSE and coronary angiography, inducible ischemia was present in 31% of patients and 30% had significant CAD, defined as >70% stenosis by visual estimation. Most of the studies described by Hage et al. [8] were performed with adenosine stress. Data published by Ragosta et al. [10] indicate that, in contrast to responses in non-diabetic, non-renal-disease control subjects and diabetic patients with normal renal function, intravenous adenosine does not cause the expected increase in coronary flow in some patients with diabetic ESRD, due to high resting basal coronary flow rates that do not increase after adenosine. Possibly, the unexpectedly low CAD detection rate in the series by Hage et al. [8] may be more a reflection of the stress modality (vasodilator stress) than the imaging technique.

Complications of diagnosis and treatment of coronary artery disease redux

Last year we cast a cursory glance on the murky topic of contrast nephropathy [11], a continuing source of clinical vexation for cardiologists and nephrologists. Reflecting the importance of this topic, a trio of clinical trials published in 2007 merit mention. Solomon et al. [12] enrolled 482 patients with estimated glomerular filtration rate (eGFR) 20 to 59 mL/min per 1.73 m² undergoing cardiac angiography or percutaneous coronary intervention. After exclusions, the authors prospectively compared the low-osmolar contrast agent iopamidol (n = 204) to the iso-osmolar agent ioxaglic acid (n = 210) in a randomized, double-blind design. All patients received prophylactic volume expansion with an isotonic sodium bicarbonate solution
(3 mL/kg/h for 1 h before angiography, 1 mL/kg/h during angiography and for 6 h after angiography). Use of pre- and post-procedure oral N-acetylcysteine (NAC) was left to the discretion of the enrolling site, as to whether all patients at a single site would receive this additional treatment (39% of the iopamidol arm and 42% of the iodixanol arm received it). The primary endpoint was a rise in serum creatinine of ≥0.5 mg/dL (44.2 μmol/L) over baseline. Nine of 204 patients (4.4%) receiving iopamidol and 14 of 210 patients (6.7%) receiving iodixanol had contrast-induced nephropathy (CIN) as defined for the primary endpoint, a non-significant difference. In 170 patients with CKD and diabetes, CIN occurred in 4 of 78 (5.1%) patients after iopamidol and 12 of 92 (13%) patients after iodixanol (P = 0.11). No patient required hemodialysis and no study-related deaths occurred. The incidence of CIN is remarkably low in this study, irrespective of use of low-osmolar or iso-osmolar contrast agents.

Briguori et al. [13] randomized 351 patients; after exclusion, they studied 326 CKD patients with serum creatinine ≥2.0 mg/dL or eGFR <40 mL/min per 1.73 m² referred for coronary or peripheral procedures. They randomly assigned 111 patients to prophylactic administration of 0.9% saline infusion (1 mL/kg/h 12 h before and 12 h after contrast administration; if LVEF <40%, infusion rate was 0.5 mL/kg/h) plus NAC, 108 patients to sodium bicarbonate infusion (154 mEq/L, 3 mL/kg/h for 1 h before contrast administration, and 1 mL/kg/hr during the procedure and 6 hours after the procedure) plus NAC and 107 patients to 0.9% saline plus intravenous ascorbic acid plus NAC. All patients received iodixanol. The primary endpoint was CIN defined as ≥25% rise in serum creatinine 48 h after contrast administration or dialysis/ultrafiltration within 5 days. The median serum creatinine concentration decreased significantly in all three groups at 48 h, raising the issue of the adequacy of the primary endpoint for CIN definition. (What exactly is being measured at 48 h, and is it an accurate surrogate for the disease process? Perhaps cystatin C would be a better surrogate marker.) Based on the primary endpoint, CIN occurred in 1.9% of the bicarbonate plus NAC group, 9.9% of the saline plus NAC group and 10.3% of the saline plus ascorbic acid plus NAC group. The authors concluded that volume expansion with sodium bicarbonate plus NAC is superior to saline with NAC alone or saline with ascorbic acid plus NAC.

Lee et al. [14] enrolled 90 patients with serum creatinine >3.5 mg/dL receiving coronary angiography; 82 patients were studied. All patients were given intravenous normal saline 1 mL/kg/h for 6 h before and 12 h after contrast administration, and 42 patients were then randomized to receive prophylactic hemodialysis (one 4-h session) and 40 patients to receive no dialysis. All patients received the nonionic contrast agent iohexol, and none received NAC or sodium bicarbonate. The baseline creatinine clearance was 13.2 ± 3.6 mL/min per 1.73 m² in the dialysis group and 12.6 ± 4.4 mL/min per 1.73 m² in the control group; 4 days after angiography, creatinine clearance was 12.8 ± 3.5 mL/min per 1.73 m² in the dialysis group and 10.4 ± 4.4 mL/min per 1.73 m² in the non-dialysis group. One patient (2%) in the dialysis group and 14 patients (35%) in the non-dialysis group required temporary clinically man-
dated post-procedure dialysis. After hospital discharge, no patients in the dialysis group and five in the non-dialysis group initiated maintenance dialysis. Interpretation of this study is clouded; in the context of other trials, it would have been invaluable to know if other measures (such as NAC or sodium bicarbonate) would ameliorate CIN in these patients with stage 5 CKD, who would actually qualify for initiation of renal replacement therapy at study entry. Nevertheless, this is a provocative pilot study that should stimulate further investigation.

The ideal clinical strategy for preventing contrast nephropathy is still a work in progress. Although we are still searching for clarity, adequate peri-procedure volume expansion seems to remain a key part of clinical practice. In our own institutional opinion-based protocol, we have previously used pre- and post-procedure NAC and intravascular volume repletion with sodium bicarbonate, contrast parsimony and iso-osmolar contrast (though some might demur on the last point); this still seems reasonable in the context of these newer studies.

Another pilot study of interest, relating to treatment of CAD in CKD patients, was published by Sajja et al. [15]. They enrolled 116 consecutive non-dialysis patients with preoperative eGFR ≤60 mL/min per 1.73 m² undergoing coronary bypass surgery, and randomized 60 to on-pump procedures and 56 to off-pump (no cardiopulmonary bypass) procedures. The authors used an unconventional definition of post-procedure acute kidney injury (20% rise in serum creatinine or 20% fall in eGFR); 62% of the on-pump and 30% of the off-pump reached this endpoint, suggesting that off-pump surgical procedures might be advantageous in patients with CKD. My own institution (reflecting my own opinion and that of our surgical consultant) has favored off-pump coronary revascularization in all CKD patients (including dialysis patients), but this issue deserves a larger clinical trial with more robust endpoints.

Acute myocardial infarction in dialysis patients

We previously reported the persistently poor long-term survival of dialysis patients hospitalized for AMI [16]. The unadjusted 2-year mortality rate for US dialysis patients after AMI changed little over the two decades spanning 1977 to 1999, remaining around 73%. We speculated that potential causes for this disturbing observation included underdiagnosis (due to atypical presentations) and undertreatment (‘therapeutic nihilism’) [5]. In attempting to understand this outcome, the Cardiovascular Special Studies Center of the United States Renal Data System (USRDS) performed a matching study of the USRDS database (n = 1 285 177), and the Third National Registry of Myocardial Infarction (NRMI 3, n = 537 444 patients in 1553 US hospitals) to identify chronic dialysis patients hospitalized for AMI in the NRMI 3 registry. We compared the clinical characteristics of 3049 dialysis patients and 534 395 non-dialysis patients with AMI [17]. We found that the diagnostic suspicion for AMI was lower in dialysis patients, with 45% (versus 21% of non-dialysis patients) not initially diagnosed with acute coronary syndrome, likely reflecting, in part, lower prevalence of chest pain
An unexpected finding was the large difference in admitting electrocardiograms. Only 19% of dialysis patients had ST elevation, compared with 36% of non-dialysis patients, and only 10% of dialysis patients versus 25% of non-dialysis patients met the accepted criteria for emergency coronary reperfusion based on electrocardiogram and other clinical variables. Acute coronary reperfusion is the cornerstone of modern AMI treatment, and the electrocardiogram defines the initial population eligible for treatment. This has tremendous implications for initial therapy, as acute reperfusion is employed only in ST-segment elevation myocardial infarction.

Our study concludes that either the mechanism of AMI is different in dialysis patients (fewer transmural infarcts) or the electrocardiogram is clinically misleading. The latter hypothesis could be tested by doing emergent angiography in a cohort of dialysis patients with AMI, as we have recently suggested. We found that therapeutic nihilism may also play a role, as only 47% of reperfusion-eligible dialysis patients received acute coronary reperfusion, compared with 75% of non-dialysis patients. Unexpected cardiac arrest occurred in 11% of dialysis patients and 5% of non-dialysis patients. Overall in-hospital mortality was 21% for dialysis patients and 12% for non-dialysis patients, with odds ratio for in-hospital mortality 1.498 (95% confidence interval 1.340–1.674) in a logistic regression model comparing dialysis to non-dialysis patients. From the clinician’s perspective, these data highlight the difficulties in making accurate diagnoses of AMI in dialysis patients and the undertreatment of this special high-risk cohort.

Coda: more clinical trials

It should be apparent that a true convergence of clinical cardiology and nephrology has occurred. This burgeoning common interest will likely be reflected in the arena of clinical investigation. In mid-September, two interesting clinical trials were published a week apart in JAMA. The first, by Jamison et al. [18] was a large-scale, multicenter, randomized, double-blind placebo-controlled trial of the effect of treatment with high doses of folic acid and B vitamins (to lower plasma homocysteine levels) in 2056 patients with advanced CKD. The authors found no difference for either the primary outcome of all-cause mortality or the secondary outcomes of myocardial infarction, stroke or amputation. This clinical trial (together with previous studies in non-CKD populations) may herald the twilight of folic acid therapy for preventing cardiovascular disease.

In the following week, Culleton et al. [19] published a preliminary study of frequent nocturnal dialysis, with 27 patients randomly assigned to nocturnal dialysis six times weekly and 25 patients assigned to conventional dialysis three times weekly. In this randomized pilot study, frequent dialysis was associated with decreased LV mass (measured by cardiovascular magnetic resonance imaging), reduction in anti-hypertensive medication and improvement in some selected ‘kidney-specific’ quality of life domains.

The efficacy of frequent nocturnal dialysis remains controversial, but the work of Culleton et al. [19] should be a catalyst for larger clinical trials. Perhaps this will signal the dawning (or more accurately, rejuvenation) of a new treatment era for dialysis patients. The new year is likely to bring new insights that will further the cardiovascular health of CKD patients (and one hopes, a new bridge over the Mississippi River in Minneapolis).

Conflict of interest statement. The author is on the scientific advisory board (SAB) of CorMedix.

References


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