Kidney Diseases beyond Nephrology

Kidney disease in cardiology

Charles A. Herzog

Abstract
This article helps to inaugurate NDT’s new section, Kidney Diseases beyond Nephrology, by focusing on the convergence of cardiology and nephrology. The clinical themes highlighted by the articles chosen for review include cardiac screening in renal transplant candidates, cardiac troponins in end-stage renal disease patients, contrast nephropathy in coronary angiography and surgical coronary revascularization across the spectrum of renal failure.

Keywords: cardiac troponins; chronic kidney disease; contrast nephropathy; coronary artery bypass surgery; end-stage renal disease; stress echocardiography

Introduction
Temporally coincident with the frigid chill descending on Minneapolis, I have been given the daunting task of helping to initiate the ‘Kidney Diseases Beyond Nephrology’ section of NDT with Dr Mann. The convergence of cardiology and nephrology is manifested by the burgeoning interest in and number of publications about cardiac disease and chronic kidney disease (CKD), particularly with the recognition of CKD as a powerful predictor of cardiovascular morbidity and mortality. From this expanding pool of recent papers dealing with cardiac disease relevant to the clinical nephrologist (and published in non-nephrology journals), several have been arbitrarily selected for a brief overview. The selection process may appear capricious, but my intent was to help frame clinical issues faced jointly by cardiologists and nephrologists. Many interesting papers were not chosen for discussion due to journal space limitations. The clinical themes highlighted by articles chosen include cardiac screening in renal transplant candidates, cardiac troponins in end-stage renal disease (ESRD) patients, contrast nephropathy in coronary angiography, and surgical coronary revascularization across the spectrum of renal failure. The arc of this review begins with the non-invasive detection of ischaemic heart disease, touches upon invasive (i.e. angiographic) issues in the evaluation of coronary artery disease (CAD) in CKD patients, and ends with one aspect of treatment (surgical revascularization) of CAD in CKD patients.

Non-invasive detection of coronary artery disease

The identification of CAD in ESRD patients is an important task for nephrologists, as cardiac disease is the single largest cause of death in dialysis patients, accounting for 43% of all-cause mortality [1]. Although the focus of cardiac screening has predominantly centred on renal transplant candidates, one could argue that this clinical strategy is flawed, as the cardiac mortality of dialysis patients who are not transplant candidates is actually considerably higher. This is partly the rationale for the US National Kidney Foundation Kidney Disease Outcomes Quality Initiative practice guideline recommending echocardiograms in all dialysis patients, irrespective of symptoms, 1–3 months after initiation of renal replacement therapy [2]. Importantly, there is an evidence-based therapy, carvedilol, which can improve the outcome for dialysis patients with dilated cardiomyopathy [3]. Serum cardiac biomarkers, notably Troponin T (cTnT), have also been promoted for screening of dialysis patients, as cTnT is a powerful independent predictor of survival in asymptomatic outpatients [2]. Potential explanations for elevated cTnT levels include cardiomyopathy (possibly apoptosis), increased left-ventricular (LV) mass [4] (and sub-endocardial ischaemia due to supply and demand mismatch), and silent obstructive CAD [5]. It has been suggested recently that minimal elevations in cTnT in the general population may be a biomarker surrogate for either prevalent cardiovascular disease or high risk for development of cardiovascular disease [6].

Screening for CAD in renal transplant candidates using dobutamine stress echocardiography (DSE) and serum cTnT is the subject of a brace of papers from
the same investigators in a prospective cohort study. The first deals with the accuracy of DSE for prediction of angiographically defined obstructive CAD, and the prediction of survival by both DSE and cTnT levels in 118 patients [7]; the second explores potential mechanisms of cTnT elevation in a nearly identical patient cohort of 126 subjects (8 patients added to the original 118) [8].

Sharma et al. [7] prospectively performed DSE, baseline cTnT measurement, and coronary angiography in 118 consecutive renal transplant candidates, of whom 46% were pre-dialysis, 39% had diabetes and 33% had diabetic ESRD. Baseline cTnT of >0.1 μg/l was arbitrarily defined as positive. DSE was performed using dobutamine plus atropine in a standard infusion protocol, and β-blockers were stopped 72 h before testing. Angiographically significant CAD was defined as >70% stenosis by visual estimate in the authors' screening process. An abnormal DSE (defined as deterioration in LV regional systolic performance with stress, compared with baseline) occurred in 31% of patients, significant CAD was found in 30%, and elevated cTnT in 26%. Allowing for the expected variation in clinical data across published studies, all three of these values are consistent with prior publications. (Interestingly, angiographically normal coronary arteries were found in 36% of subjects). The sensitivity, specificity and positive and negative predictive values for DSE in detecting angiographically defined CAD (>70% visual stenosis) were respectively 88, 94, 86 and 95%. The sensitivity, specificity, and positive and negative predictive values of abnormal cTnT levels for prediction of CAD were respectively 54, 62, 40 and 74%. Patients were followed for 1.32 ± 0.48 years. Long-term survival was not predicted by DSE result; however, abnormal cTnT was a predictor of mortality. A cTnT cut-off value of 0.08 μg/l predicted mortality with a 75% sensitivity and 76% specificity. As some patients with CAD understandably received subsequent coronary revascularization triggered by the testing, some of the long-term survival data are difficult to interpret, due to confounding. In this study, DSE was an accurate predictor of CAD, but not of survival. In contrast, elevated cTnT levels were predictive of survival, but not of CAD severity.

The later paper by Sharma et al. [8] further explores the aetiology and clinical significance of elevated serum cTnT levels in renal transplant candidates, using cTnT cut-off values of 0.04 and 0.10 μg/l. The authors found that subjects with elevated cTnT levels were more likely to have LV enlargement, decreased LV systolic function (although their entire cohort was characterized by normal systolic function with a mean LV ejection fraction of 67 ± 14%), and increased estimated LV filling pressures (which in this population would be a potential surrogate for LV diastolic dysfunction in patients with normal LV ejection fraction evaluated at the time of euvaloaemia), and to be diabetic. As suggested in the earlier study, the authors did not find a strong association of cTnT elevation and CAD burden.

Although I am a strong proponent of DSE for CAD screening in ESRD patients (our echocardiography laboratory at Hennepin County Medical Center in Minneapolis has performed about 1200 DSE studies in dialysis patients), one major caveat is the importance of institutional expertise, and the potentially wide variation in diagnostic accuracy across centres. If coronary angiography is used as the benchmark for defining CAD, DSE accuracy probably exceeds pharmacologic stress nuclear imaging for diagnosing CAD in ESRD patients [9]. A second critical issue relates to the rationale for CAD screening in renal transplant candidates. As the evidence base for pre-emptive or prophylactic revascularization in these patients is weak, one could question the need for prediction of significant angiographically defined obstructive CAD, particularly if the patients are already receiving optimal medical therapy [9]. The role of medical therapy, notably β-blockers, in reducing peri-operative cardiac risk in the general population was (again) raised in a recent study by Poldermans et al. [10]. The potential long-term benefit of prophylactic β-blockers in ESRD patients who are not receiving β-blockers for other indications merits further investigation.

Complications of invasive detection of coronary artery disease and coronary intervention: contrast nephropathy

Contrast nephropathy is the Achilles' heel of coronary intervention in CKD patients not requiring dialysis. An entire issue of NDT could easily be devoted to this murky topic. From my perspective as a cardiologist working with CKD and CAD patients, it is a problem commonly faced in clinical practice, and thus merits attention, even if only in a limited fashion, for this review. Fortunately, three articles have been published in 2006, which provide an excellent background for the topic of preventing contrast nephropathy: a review by Barrett and Parfrey [11], a meta-analysis by McCullough et al. [12] focusing on the isosmolar agent iodixanol, and a meta-analysis on a range of interventions by Pannu et al. [13]. These studies bracket the range of opinion on this controversial topic, and should be read in tandem. The most sceptical appraisal is offered by Barrett and Parfrey [11], who advise pre-procedure hydration with saline but do not recommend intravenous sodium bicarbonate or N-acetylcysteine at the present time, nor do they preferentially select the isosmolar agent iodixanol over low-osmality radiocontrast media. McCullough et al. [12] conclude that the use of iodixanol to reduce contrast nephropathy is indicated in high-risk patients (those with CKD or diabetes mellitus), and Pannu et al. [13] offer a management algorithm that includes N-acetylcysteine or ascorbic acid in high risk patients, pre-procedure hydration with intravenous saline or sodium bicarbonate administration, low or isosmolar contrast,
and post-procedure intravenous hydration. All three papers endorse parsimony in contrast administration and none recommend prophylactic haemofiltration.

As I have pointed out in a previous review [9], clinicians must routinely apply imperfect data to clinical practice. Contrast nephropathy gives clinicians much to be confused about. I agree with several critical comments by Pannu et al. [13]. The usual definition (25% rise above baseline serum creatinine or absolute increase of 0.5 mg/dl [44.2 μmol/l]) seems a bit arbitrary. Why exactly is contrast nephropathy associated with adverse outcomes, particularly long-term mortality? If it is merely a surrogate for other pathological processes, our attention might be misdirected toward a risk marker and not a true cause of morbidity and mortality (like homocysteine, but that’s grist for another review). In my own practice, the opinion-based approach used in our cardiac catheterization laboratory for coronary angiographic studies in non-dialysis CKD patients is pre- and post-procedure N-acetylcysteine, pre-procedure intravenous hydration with sodium bicarbonate, optional right heart catheterization to avoid unapparent hypovolemia (with saline hydration to a target pulmonary capillary wedge pressure of 16–18 mmHg), contrast parsimony (including staging of complex multivessel percutaneous coronary intervention [PCI]) using iodixanol and post-procedure hydration. We omit hydration protocols in dialysis patients. Finally, consistent with our strategy of contrast parsimony, all of our CKD patients receive prior echocardiographic studies to avoid unwarranted left ventriculography, and to detect clinically unsuspected valvular disease or cardiomyopathy.

Jo et al. [14] provide additional support for the use of iodixanol in CKD patients. In this prospective randomized double-blind trial performed in Korea, patients electively referred for coronary angiography with or without PCI with creatinine clearance ≤60 ml/min and not on dialysis were assigned to receive either iodixanol (a non-ionic dimeric isosmolar radiocontrast medium; n = 151) or ioxaglate (an ionic, dimeric low-osmolar radiocontrast medium; n = 149). Both groups received intravenous hydration with saline, but not N-acetylcysteine. The primary endpoint of the trial was incidence of contrast nephropathy, defined as a relative increase in serum creatinine of 25% or absolute increase of 0.5 mg/dl (≥44.2 μmol/l). A total of 11 patients in the iodixanol arm and 14 in the ioxaglate arm were excluded after randomization, mostly for absence of mandated follow-up laboratory testing. Eleven patients (7.9%) in the iodixanol arm and 23 (17.0%) in the ioxaglate arm had the prespecified rise in serum creatinine within 2 days of contrast administration. The odds ratio for contrast nephropathy was 0.42 (95% confidence interval 0.19, 0.89) for iodixanol vs ioxaglate. In patients with severe renal impairment (creatinine clearance <30 mg/dl), the incidence of contrast nephropathy was 12.5% in the iodixanol arm (2 of 16 patients) vs 53.3% in the ioxaglate arm (8 of 15 patients).

In this small (underpowered) study, there was no difference in the clinically important composite safety endpoint (death, myocardial infarction, revascularization, cerebral infarction or dialysis) based on adverse events identified during 30-day follow-up, with three adverse events in each group. I suspect that the authors of the three aforementioned articles [11–13] would not alter their respective conclusions if presented with the additional data described by Jo et al. [14].

Observational studies on chronic kidney disease and outcome after surgical coronary revascularization

This brings us to our last topic, observational studies on CKD and survival after surgical coronary revascularization. A recurring theme in these studies is the predictive value of impaired renal function for morbidity and mortality. However, none of the studies clarifies the extent to which the mortality hazard apportioned to low estimated glomerular filtration rate (eGFR) is merely a surrogate measure of disease burden, and how much is the actual disease. Three complementary studies on the association of renal function and outcome after surgical coronary revascularization merit mention: the analysis by Cooper et al. [15] of 30-day outcome related to eGFR, based on the simplified Modified Diet in Renal Disease (MDRD)-equation, in the massive Society of Thoracic Surgeons (STS) National Adult Cardiac Database; the study by Hillis et al. [16] of eGFR by simplified MDRD equation and long-term survival; and the report by Brown et al. [17] on the association of perioperative increases in serum creatinine and 90-day mortality.

Cooper et al. [15] analysed 483 914 patients in whom eGFR could be calculated or who were on dialysis, receiving isolated coronary artery bypass surgery, from 1 July 2000 to 31 December 2003, in the STS database, for the primary outcome of 30-day mortality and secondary outcomes of morbidity, including stroke and new acute dialysis. (The main limitation of the STS database is that it contains no data for long-term survival.) In their study, 22% of patients had eGFR ≥90 ml/min/1.73 m², 51% had eGFR 60–89, 24% 30–59, 2% <30 and were not on dialysis, and 1.5% required dialysis. The unadjusted mortality for the five subgroups of renal function were respectively 1.3% (eGFR ≥90), 1.8, 4.3, 9.3 and 9.0% (on dialysis). Stroke occurred in respectively 0.9, 1.3, 2.4, 3.5 and 3.3% of patients. Acute new dialysis was required in 0.2, 0.5, 1.8 and 10.9% of each group (prior dialysis excluded). The finding that unadjusted survival is comparable for severe non-dialysis-dependent CKD and dialysis patients is consistent with prior publications. In a multivariate model adjusted for 27 other clinical risk factors, compared with eGFR ≥90 ml/min/1.73 m², odds ratios for death (95% confidence interval) were 1.02 (0.96, 1.09) for eGFR 89–60 ml/min/1.73 m², 1.55 (1.45, 1.65) for eGFR 30–59, 2.87 (2.61, 3.16) for eGFR <30, and 3.82 (3.45, 4.25) for dialysis patients.

Hillis et al. [16] reported on a cohort of 2067 patients in Aberdeen, UK, not requiring dialysis and
undergoing coronary artery bypass surgery 1 April 2000, to 31 March 2004. Of the participants, 11% had concomitant major cardiovascular procedures. The association of eGFR and the primary outcome of mortality were analysed. In the cohort, 37% of patients had an eGFR of <60 ml/min/1.73m², and this sub-set was hospitalized a median of two days longer after surgery, accounted for 70% of deaths within 30 days after surgery, and had a 2-fold risk of long-term mortality. In a multivariate model, an eGFR increase of 10 ml/min was associated with a 20% decrease in long-term mortality (hazard ratio 0.80; 95% confidence interval 0.72, 0.89).

Brown et al. [17] reported on 1391 patients (dialysis excluded) undergoing isolated coronary artery bypass surgery in the Northern New England Cardiovascular Disease Study Group (US) in 2001. The purpose of the study was to assess the relation between pre-operative serum creatinine and maximum post-operative creatinine compared with survival. The primary outcome was 90-day mortality, which was 1.5% for patients with <25% post-operative rise in serum creatinine, 3.1% for 25-49% rise, 12.2% for 50–99% rise and 30.8% for ≥100% rise. In an adjusted hazard model, with <25% rise as reference, the hazard ratio for 90-day mortality in patients with 25 to 49% rise in creatinine was 1.80 (95% confidence interval 0.73, 4.44), for 50–99% rise 6.57 (3.02, 14.27), and for ≥100% rise in creatinine 22.1 (11.25, 43.39).

Conclusion

Patients with CKD are a high risk population for cardiovascular morbidity and mortality. Non-invasive stress imaging, notably DSE, can predict CAD burden in ESRD patients. Serum levels of cardiac biomarkers (such as cTnT) are linked to all-cause mortality, but not necessarily to CAD severity in dialysis patients. Impaired renal function is correlated with increased all-cause mortality, including in the setting of contrast nephropathy after coronary angiography and surgical coronary revascularization. Less clear is the underlying cause of this increased mortality, and whether renal impairment is simply a surrogate for disease or actually a disease process to further target with interventions to improve outcome. In the instance of contrast nephropathy, an array of prophylactic therapeutic interventions has been proposed and validated with varying levels of evidence.

The convergence of clinical cardiology and nephrology is a relatively recent phenomenon. As this cursory selection of recent publications has demonstrated, there is still much to learn about the relation of CKD across the spectrum of renal failure and cardiovascular disease.

Conflict of interest statement. None declared.

References

14. Jo SH, Youn TJ, Koo BK et al. Renal toxicity evaluation and comparison between visipaque (iodixanol) and hexabrix (ioxaglate) in patients undergoing renal insufficiency undergoing coronary angiography. The recovering study: a randomized controlled trial. J Am Coll Cardiol 2006; 48: 924–930

Received for publication: 9.11.06
Accepted in revised form: 9.11.06