Mini-Review

Biomarkers and Cardiac Disease in Patients with End-Stage Renal Disease on Dialysis

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Abstract
Very soon after troponin was introduced to routine clinical use in the mid-1990s, it was observed that troponin T was often increased in the blood of asymptomatic patients undergoing chronic dialysis for end-stage renal disease. Observation of these patients showed that the presence of troponin T in blood was predictive of a worse outcome for these patients.

Cardiac disease is the major cause of death in dialysis patients. This review considers the heterogeneous cardiac disease that is found in these patients and reviews the role of cardiac biomarkers in identifying patients at risk of an adverse outcome.

Introduction

There is a high morbidity and mortality amongst patients on dialysis. Australia has amongst the best survival figures in the world for patients on dialysis, and, even here, the overall death rate is 15.0 per 100 patient years, although the death rate is much higher in patients aged over 65 years.[1]

The major cause of death in dialysis patients is cardiovascular disease, but many of these persons at risk are asymptomatic. Detectable troponin T in the blood of dialysis patients was reported from the time that troponin T assays became commercially available and initially these were thought to be false positive results as was often seen with creatine kinase-MB.[2] However, good outcomes data quickly showed that this association was real.[3,4]

Besides troponin T, a number of other biomarkers have been shown to be predictive of mortality in dialysis patients, including C-reactive protein (CRP),[5] brain natriuretic peptide (BNP)[6] and NT-proBNP (N-terminal fragment of the propeptide),[5,7] and more recently troponin I.[5,8]

This paper will review the nature of cardiac disease in dialysis patients and provide information on the current use and meaning of cardiac biomarkers in these persons.

Cardiac Disease in Dialysis Patients

Cardiac disease is common in persons undergoing chronic dialysis. As a consequence of renal failure, sodium retention occurs with consequent fluid retention, hypervolaemia and hypertension.[9,10] The hypertension is frequently potentiated by sympathetic overactivity.[11] Left ventricular hypertrophy is common in dialysis patients with more than 50% of patients having this condition,[12,13] and myocardial ischaemia and heart failure frequently occur as a result.[14] However, traditional risk factors for cardiovascular disease seem to be relatively less important in this patient group and novel risk factors such as protein energy-wasting, endothelial dysfunction, oxidative stress and vascular calcification are more prevalent and appear to be more important in identifying cardiovascular risk.[15]

On top of this chronic cardiac disease burden, sudden death is common in these patients. Dialysis by itself can cause acute hypotension[16] and myocardial ischaemia.[17] Analysis of time of death shows a higher occurrence around the time of dialysis and when the time between dialysis is lengthened (commonly over the weekend), and myocardial ischaemia and electrolyte abnormalities are thought to be important factors.[18,19]

The prevalence of renal failure is low in children, but is associated with a 700-fold increase in mortality. As in adults, hypertension and left ventricular hypertrophy are common findings.[20]

Prognostic Biomarkers in Dialysis Patients

Desai *et al.* have recently performed a systematic review

of more than 100 reported studies which looked at the relationship between laboratory-based outcome measures and mortality.[21] They found that markers of dialysis adequacy, inflammatory markers, nutritional markers and troponin T were important predictors of mortality in dialysis patients, but that troponin T had the highest relative risk. These data are shown in Table 1 below.

Unsurprisingly dialysis (in)adequacy is a strong predictor of mortality in dialysis patients.[22] Adequacy of nutrition is also an important predictor of survival with a serum albumin concentration <35 g/L being associated with a much higher mortality rate.[23,24] Prealbumin, which has a substantially shorter half-life than does albumin, was an even more powerful predictor of poor outcomes.[25]

Chronic inflammation is a part of advanced renal disease and especially dialysis, and markers of inflammation such as interleukin-6 (IL-6), tumour necrosis factor (TNF) and especially CRP are predictive for mortality, and because albumin is a negative acute phase reactant it is hypothesised that a low albumin concentration may be secondary to the chronic inflammation that increased CRP is identifying.[26]

Cardiac Biomarkers in Dialysis Patients

Traditional markers of risk of cardiac disease such as homocysteine and cholesterol were not identified as significant contributors to mortality in dialysis patients when studies were pooled.[21] This review also found that BNP was not a significant contributor to mortality but cautioned that a very small number of studies had contributed data to their analysis. A further consideration as to reasons for the non-significance of BNP might have been that only BNP was measured and not NT-proBNP which we have found to be more informative.[27]

Cardiac troponin – in particular troponin T – is an important predictor of mortality in asymptomatic patients undergoing chronic dialysis.[4,28] It must be emphasised that this is risk prediction outside the more usual setting of the acute coronary syndrome. In this setting, troponin I appeared to be less informative than troponin T.[29]

Differences between Troponin T and Troponin I in Dialysis Patients

Innumerable studies have shown that troponin T and troponin I are equally informative when patients are being assessed for the acute coronary syndrome.[30,31] Renal failure is one of the few areas where there appears to be some difference in performance between these two analytes. Troponin T but not troponin I is more reliably detected in asymptomatic dialysis patients who are not experiencing an acute coronary syndrome, and this troponin T increase is predictive of a poor outcome – either myocardial infarction or death.[32]

Desai *et al*[33] showed that troponin T fragments identified using multiple monoclonal antibodies directed against different troponin T epitopes were present in the blood of patients undergoing chronic dialysis. They demonstrated that these fragments increased as duration of dialysis increased and hypothesised that troponin T fragments are normally cleared by the kidney and that renal impairment causes accumulation of these fragments. Studies looking at clearance of troponin

Table 1. Which biomarkers predict mortality in patients on dialysis?

Type	Significant Predictor	Non-significant Predictor
Inflammatory	TNF IL-6 CRP	
Anaemia	Hematocrit	
Acid/base		Bicarbonate
Nutrition	Albumin Prealbumin	Lymphocyte count
Small molecule clearance	Kt/V_{urea} URR	
Cardiovascular	Troponin T	Homocysteine Natriuretic peptides Cholesterol
Mineral metabolism		Ca x P PTH

These data derived from Desai *et al*.[21] TNF, tumour necrosis factor-α; IL-6, interleukin 6; CRP, C-reactive protein; Kt/V_{urea}, dialyzer clearance of urea; URR, urea reduction ratio; Ca x P, the product of the concentrations of serum calcium and phosphate; PTH, parathyroid hormone.

I in patients with and without renal impairment found no difference in half-life of clearance,[34] suggesting that it is a difference in renal clearance which explains why troponin T but not troponin I may be increased in asymptomatic dialysis patients.

Diris et al[33] raised the possibility that troponin T accumulation in dialysis patients might reflect physiological turnover of cardiac myocytes. However, this ignored the well established body of evidence that there is an inverse correlation between troponin T concentration and prognosis in dialysis patients.[28,35] As discussed above, cardiac disease in dialysis patients is heterogeneous, but it appears that the many forms of asymptomatic cardiac disease in these patients are characterised by a low-level release of troponin T which accumulates in the circulation.

More recent evidence suggests that this apparent disparity in performance between troponin T and troponin I may be less than initially believed. Studies using newer troponin I assays (Abbott Architect and Siemens Centaur) in 2005 found a similar performance to troponin T. These data are shown in Table 2. At the limit of detection, both troponin I assays and the troponin T assay identified more than 90% of patients at risk. At concentrations corresponding to the 20% CV both troponin T and I assays identified more than 80% of patients at risk and it was only at concentrations corresponding to the 10% CV that troponin T identified more patients at risk (75%) than the troponin I assays (54 and 59% respectively).[8] It should be noted that an expert group have just recommended reporting troponin to a concentration corresponding to the 20% CV rather than the 10% CV as is the current recommendation,[36] and it is likely that future revisions of the definition of myocardial infarction will include this recommendation. In this context it appears that there is little difference in the ability of troponin T and troponin I assays to identify dialysis patients at risk of an adverse event.

BNP and NT-ProBNP in Dialysis Patients

The systematic review by Desai *et al*[21] covering the period to 2007 reported that BNP was not significantly associated with mortality in asymptomatic dialysis patients. However, there have been several reports since then indicating that both BNP and NT-proBNP had predictive value in this patient group.[27,37,38,39] It appears that NT-proBNP has better predictive value than BNP,[27] and this molecule has better predictive value than troponin T in short-term followup (<3 years).[27,37] However, of great interest, is that troponin T replaces NT-proBNP as the best predictor of prognosis as time since sample collection increases. In one study NT-proBNP was the best predictor at 30 months, but at 45 months troponin T provided better prognostic information.[40] Given that cardiac disease in dialysis patients is very heterogeneous, presumably the two molecules are identifying different subpopulations.

High Sensitivity Troponin Assays in Dialysis Patients

The newly available high sensitivity troponin assays are causing us to rethink the significance of troponin in blood as assessment of apparently healthy populations showed the presence of troponin – both T and I – in the blood of a large proportion of healthy individuals.[41,42]

To date, there is little published literature relating to use of high sensitivity troponin assays in dialysis patients.[40,43] Comparison of the standard and the high sensitivity troponin T assays in these papers, showed that 63% and 76% respectively of dialysis patients had detectable troponin with the old assay but both papers reported that 100% of patients had detectable troponin T with the high sensitivity assay. The 99th percentile for a healthy reference population for the high sensitivity troponin T assay is 16 ng/L.[43] We found that all patients with a troponin T <24.15 ng/L survived at 46 months of followup, whilst the mortality of those with troponin T >24.15 ng/L was over 50%.[40] The fact that many persons with a troponin T concentration above the 99th percentile for a healthy

Table 2. Ability of different troponin assays to identify dialysis patients who had an adverse outcome within two years of blood sampling.

	Troponin T	**Troponin I**	
	Roche	Abbot Architect	Siemens Centaur
LOD	92.9%	96.4%	100%
20% CV	89.3%	82.1%	85.2%
10% CV	75.0%	53.6%	59.3%

Adapted from Hickman *et al.*[8] The percentages refer to the proportions of patients with an adverse outcome (cardiac death, death from any cause, myocardial infarction) who had a troponin concentration greater than the specified cut-off: LOD, limit of detection; 20% CV, the concentration determined with a CV (coefficient of variation) of 20%; 10% CV, the concentration determined with a CV of 10%.

population survive is probably a reflection of advanced renal disease with dialysis being an inflammatory state.

Summary

In summary, cardiac disease is common amongst persons undergoing dialysis for chronic renal failure and there is a high mortality in this group. A number of biomarkers, but particularly troponin and (NT-pro)BNP are strong predictors of mortality in these persons. To date, studies on these patients have been predominantly descriptive. When attempts are made to aggressively treat these persons objectively identified to be at risk, it will be of great interest to see whether the morbidity and mortality can be reduced.

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