Cardiac Biomarkers in Haemodialysis Patients: The Prognostic Value of Amino-Terminal Pro-B-Type Natriuretic Peptide and Cardiac Troponin T

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Key Words

Haemodialysis • Troponin • Amino-terminal pro-B-type natriuretic peptide • Cardiac biomarker • Hypervolaemia • Cardiovascular mortality

Abstract

Cardiac biomarkers such as amino-terminal pro-B-type natriuretic peptide (NT-proBNP) and cardiac troponin T (cTNT) provide information on cardiovascular morbidity and mortality in patients with normal renal function. In a considerable number of chronic haemodialysis patients, both biomarkers – NT-proBNP and cTNT – are elevated despite the absence of cardiac ischaemia. The elevation of cardiac biomarkers in chronic haemodialysis patients is of prognostic value with respect to cardiovascular morbidity and mortality. They provide a useful rationale for the screening of occult cardiac disease and optimization of the dialysis procedure with respect to volume control.

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Prevalence of Elevated Cardiac Troponin T and Amino-Terminal Pro-B-Type Natriuretic Peptide in Chronic Haemodialysis Patients

It is well known that cardiovascular events are the most common cause of death in end-stage renal disease. Consequently, patients with end-stage renal disease are considered to be in the highest risk group for subsequent cardiovascular events. Indeed, the annual risk of cardiovascular death is greater for a 30-year-old patient on dialysis than for an 80-year-old with normal renal function [1]. Cardiac troponin T (cTNT) is the most reliable biomarker for the diagnosis of acute myocardial ischaemia with or without ST segment elevation [2]. cTNT is exclusively expressed in cardiomyocytes and is released into the circulation after irreversible myocardial damage.

The cardiac biomarkers amino-terminal pro-B-type natriuretic peptide (NT-proBNP) and cTNT are often elevated in patients with various degrees of chronic renal failure and in end-stage renal disease without clinical evidence of acute ischaemia [3, 4]. In previous studies, the incidence of pathologically elevated cTNT plasma levels prior to dialysis sessions varied between 20 and 53% [5–7]. This wide range is explained by different study populations, in particular with respect to the prevalence of

diabetes. Apple et al. [4] found an elevation of cTNT in 85% of their study population with a prevalence of 46% in patients with diabetes. In a comprehensive multicentre study in the Netherlands (Netherlands Cooperative Study of the Adequacy of Dialysis), 847 haemodialysis and peritoneal-dialysis patients were examined, with two thirds of the patients on haemodialysis [8]. Of these patients, 22.2% had a cTNT of 0.05–0.10 ng/ml (with a detection limit according to the manufacturer of <0.04 ng/ml), and 11% had a cTNT value above 0.10 ng/ml. In this Dutch study population, 20.6% of patients had diabetes, 10.9% a history of myocardial infarction and 13.6% a history of peripheral occlusive disease. A recent single-centre study from our unit revealed cTNT levels of above 0.03 ng/ml in 40% of the haemodialysis patients, with a prevalence of diabetes in 50% [9]. Several explanations for cTNT elevation in uraemic patients, although controversial, have been proposed, for example increased left-ventricular-wall tension, acute or chronic volume overload, silent plaque rupture in the presence of diffuse coronary atherosclerosis and apoptosis of cardiomyocytes [5, 10]. Other explanations are glycosylation of end products followed by loss of cardiac membrane integrity in patients with diabetes, cardiomyocyte-capillary mismatch in uraemic patients resulting in lower ischaemia tolerance of the heart [11], and the impaired renal clearance of the proteolytic products of troponin T [12].

B-type natriuretic peptide and NT-proBNP, an active metabolite of proBNP, are often increased in patients with renal insufficiency and are indicators for underlying cardiac disease, such as coronary artery disease and left-ventricular hypertrophy [13, 14]. Increased NT-proBNP plasma levels are found in a considerable proportion of patients with end-stage renal disease. Apple et al. [4] found increased NT-proBNP levels in 99% of 399 patients with end-stage renal failure. A smaller study confirmed excessively increased NT-proBNP concentrations in haemodialysis patients, with a mean value of roughly 25,000 pg/ml [15]. A possible explanation could be the high prevalence of left-ventricular dysfunction; however, even in dialysis patients without acute cardiovascular events and severe left-ventricular failure, NT-proBNP plasma levels were above the normal range (defined for non-renal patients) [9]. We showed in a cohort of 134 chronic haemodialysis patients that median NT-proBNP was 4,524 pg/ml, with interquartile ranges between 2,000 and 10,250 pg/ml, compared to a reference level of <125 pg/ml in healthy volunteers. Besides cardiac dysfunction, there are other factors which influence plasma NT-proBNP levels. Female gender and age were strong predictors for higher

NT-proBNP levels [16]. Moreover, it is likely that renal function influences plasma NT-proBNP levels [17]. NT-proBNP is mainly excreted by glomerular filtration, and therefore the level is particularly high in oligo-anuric haemodialysis patients [9]. It is of note that heterophilic antibodies may interfere with NT-proBNP immunoassay measurements [18], and dialysis patients are more likely to develop antibodies as they often receive multiple blood transfusions. However, in the last few decades, the number of blood transfusions because of renal anaemia has been reduced, since erythropoietin substitution is now widely available.

NT-proBNP and cTNT and Their Relation to Volume Load in Haemodialysis Patients

Cardiac biomarkers are elevated in haemodialysis patients for various reasons. Haemodialysis patients are often afflicted with asymptomatic coronary artery disease, left-ventricular dysfunction or diastolic dysfunction. Several recent studies have analysed the association between left-ventricular hypertrophy and cardiac biomarkers in haemodialysis and peritoneal-dialysis patients [13, 16, 19]. Almost all studies showed a positive correlation with respect to left-ventricular mass and dysfunction and cTNT [5, 10, 19]. Experimental studies documented a relationship between left-ventricular hypertrophy and myocardial ischaemia, due to an impaired perfusion of the subendocardial wall [20].

Cardiac tissue remodelling is induced not only by ischaemia but also by hypervolaemia. It could be speculated that chronic hypervolaemia is followed by left-ventricular hypertrophy and diastolic dysfunction. In a recent experimental model, it was demonstrated that chronic overload induces cardiac muscle fibre remodelling [21]. In addition, increased myocardial dilatation in the state of acute and chronic hyperhydration may lead to secretion of cTNT and NT-proBNP by membrane leakage. Furthermore, it is likely that the dialysis procedure itself influences the cTNT and NT-proBNP levels, either by haemoconcentration or by the type of dialysis. In haemofiltration, haemoconcentration followed by an increase in cardiac biomarkers is supposed, whereas in haemodialysis and haemofiltration, cardiac biomarkers may be affected by convection. In addition, the use of high-flux instead of low-flux dialysis membranes results in better clearance of larger molecules. Therefore, with high-flux dialysers a better clearance of cardiac biomarkers is possible [15, 22]. In a recent study, cTNT proved to

be an independent predictor of cardiovascular congestion in chronic peritoneal-dialysis patients. In determining the risk of cardiovascular congestion, troponin T appeared to be even more important for prognosis than left-ventricular myocardial infarction or the left-ventricular ejection fraction, and was identified as a predictor of circulatory overload, which is a frequent complication in peritoneal-dialysis patients [19]. NT-proBNP was linked to the left-ventricular mass index and left-ventricular ejection fraction in peritoneal-dialysis patients, but the hydration status was not reflected adequately by NT-proBNP [13]. Another interesting parameter in peritoneal-dialysis patients is residual renal function, which is essential for adequate peritoneal dialysis, especially since persisting diuresis has a significant impact on cardiac biomarkers such as cTNT and NT-proBNP [9].

cTNT and NT-proBNP – Cardiac Biomarkers with Prognostic Value in Haemodialysis Patients?

Cardiovascular disease is the most common cause of death in patients with end-stage renal disease (United States Renal Data System data). The identification of haemodialysis patients at high risk for cardiac complications is challenging, and cardiac biomarkers could be helpful for risk stratification. In dialysis patients listed for renal transplantation, measurement of cardiac biomarkers is an especially useful tool for risk stratification, since a high percentage of these asymptomatic and mostly young patients in a relatively good medical condition have elevated troponin T (38% listed vs. 52% non-listed haemodialysis patients) [23].

In the past, the prognostic usefulness of troponins in patients with impaired renal function was unclear, and conflicting results were published owing to insensitive assays which cross-reacted with skeletal troponin [24]. Recent data have shown that the presence and magnitude of cTNT are independent variables with respect to morbidity and mortality in haemodialysis patients [25–27]. Apple et al. [4] demonstrated a 2- to 5-fold risk of death for haemodialysis patients with elevated cTNT unadjusted for other cardiovascular mortality risk factors. After adjustment for the independent risk factors, the risk of death remained 2- to 4-fold. In a more recent study, a Cox regression analysis revealed increased hazard risk ratios for 1-year mortality of 2.2 for troponin plasma levels of 0.05–0.10 ng/ml and 3.0 for cTNT levels >0.10 ng/ml, after adjustment for traditional risk factors [8]. Similar results are shown in various other studies [5–7, 10].

Fig. 1. Patient survival according to cTNT and NT-proBNP levels. In 34 patients both cTNT and NT-proBNP were above the thresholds, in 100 patients at least one parameter was below the thresholds (thresholds: cTNT >0.026 ng/ml, NT-proBNP >5,300 pg/ml). Reproduced by courtesy of Blackwell Publishing, Edinburgh, UK.

In a cohort of 134 patients with a longitudinal follow-up of 36 months, we found cardiovascular events in 55.2% of cases (48.6% death, 45.9% myocardial infarction or coronary intervention, 23.1% peripheral arterial disease with surgical intervention or apoplexy/carotid artery surgery) and studied the prognostic value of cTNT and NT-proBNP [9]. Plasma cTNT levels were significantly higher in patients with the composite endpoint consisting of cardiovascular, peripheral vascular and cerebrovascular events. Twenty-three patients died from cardiac events (myocardial ischaemia, sudden cardiac death). Patients with cardiovascular death had significantly higher cTNT levels prior to haemodialysis, i.e. cTNT 0.040 (<0.01–0.177) versus 0.018 (<0.001–0.047) ng/ml; $p < 0.05$ [9].

With respect to NT-proBNP, a recent study done with 987 haemodialysis patients found that this is a predictive marker for cardiovascular events and cardiovascular mortality with initially stable coronary artery disease [28]. There is only scarce information on NT-proBNP and its prognostic value in patients with progressive or terminal renal failure [27, 29, 30]. Increased NT-proBNP plasma levels are significant indicators of coronary artery disease and left-ventricular hypertrophy in asymptomatic chronic kidney disease patients prior to dialysis [14]. As mentioned above, NT-proBNP levels are elevated in nearly all dialysis patients, but stratification by tertiles can identify patients who are at especially high risk. In a

study by Apple et al. [4], tertile analyses of NT-proBNP concentrations were significantly predictive for cardiac death, and the area under the receiver operating characteristic (ROC) curve was equivalent or better than for any other biomarker, for example high-sensitivity C-reactive protein, troponin I or troponin T. Recently, we showed that NT-proBNP, despite its elevation in all 134 haemodialysis patients, is a prognostic factor for cardiovascular morbidity and mortality [9]. In a longitudinal follow-up of 36 months, 23 out of 134 patients died from cardiovascular events; all of them had higher NT-proBNP levels prior to haemodialysis than patients without cardiovascular events [9,649 (2,132–19,558) vs. 4,026 (1,864–8,226) pg/ml; $p < 0.05$]. With respect to significant volume overload, we demonstrated by ROC analysis a cTNT threshold of 0.026 ng/ml and an NT-proBNP threshold of 5,300

pg/ml. Especially patients with both cTNT and NT-proBNP above the hypervolaemia detection threshold were more likely to die earlier (52.9 vs. 18%; fig. 1).

In summary, plasma levels of cTNT are elevated in approximately 20–50% of patients with end-stage renal disease, and NT-proBNP levels are increased in nearly all asymptomatic chronic haemodialysis patients. Besides the high prevalence of cardiac diseases in these patients, the status of renal failure (especially oligo-anuria) and volume overload influences both parameters. These facts must be taken into account when interpreting cTNT and NT-proBNP levels. Increased NT-proBNP and cTNT are strongly associated with adverse outcomes in end-stage-renal-disease patients undergoing haemodialysis. Both parameters are useful tools for risk stratification in chronic haemodialysis patients.

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