Are natriuretic peptides a reliable marker for mortality in ESRD patients?

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Introduction

Among the markers of cardiovascular diseases (CVDs) studied in the last 15–20 years, both B-type natriuretic peptide (BNP) and its N-terminal fragment (NT-proBNP) represent a very interesting group of markers. Several studies have demonstrated their role in the development of cardiac failure and other CVD, and BNP has been introduced in the interventional guideline algorithms proposed by the main scientific societies [1,2]. These guidelines suggest analysing BNP and NT-proBNP in untreated but symptomatic patients, and levels of BNP >400 pg/mL and NT-proBNP >2000 pg/mL are considered suggestive for chronic heart failure.

It is well known that CVDs are the most frequent cause of morbidity and mortality in patients with chronic kidney disease (CKD) [3], and individuals with CKD have up to 20-fold greater risks of cardiac death, compared to age- and sex-matched controls without CKD.

It has also been demonstrated that plasma levels of BNP are increased both in non-dialysis- and dialysis-dependent CKD patients. BNP is a reliable test to diagnose significant structural or functional CVDs even in children [4].

Natriuretic peptides (NPs) offer the potential for early detection and risk stratification of CVD in patients admitted to the emergency department [5]. These markers could also be useful for CKD patients asymptomatic for CVD [6].

In this issue of the Journal, Paniagua et al. [7] publish an interesting paper, highlighting what several previous papers demonstrated mainly in the general population, i.e. both BNP and proBNP plasma values in CKD stage 5D patients are directly correlated with extracellular fluid expansion and left ventricular myocardial mass, and are inversely closely correlated with residual renal function [8–11]. High NP values are also associated with inflammation, while there is no clear correlation with obesity and diabetes [12,13]. Besides, NT-proBNP levels are both markers of myocardial damage and fluid overload [9,10].

In the family of NPs, NT-proBNP seems to be the best predictor of clinical outcome and marker of extracellular fluid overload. In fact, the synthesis of NT-proBNP in the left ventricle represents a response to stimuli requiring greater ventricular work. This peptide is larger and has a longer half-life than BNP (the active form), making its measurement easier and also less dependent on acute changes, while this is an important factor affecting the concentration of other NPs [14].

During the last years, the value of the NT-proBNP plasma concentration has been a ‘hot topic’ not only as an independent predictor of general and cardiovascular mortality but also as a marker of fluid control in dialysis patients. The role of NT-proBNP as a predictive marker of clinical outcome in patients on dialysis has been proven, but there are no data about its interaction with fluid volume control and dialysis modality. The aim of the paper from Paniagua et al. [6] was just to demonstrate the interaction between NT-proBNP, fluid volume control and different dialysis modalities.

Role of NPs in dialysis patients

The authors correctly underlined that the different dialysis modalities, such as haemodialysis (HD), continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD), have a different impact on fluid volume control, thus indirectly affecting the NT-proBNP concentration values.

By ultrafiltration, HD causes contraction in the extracellular fluid volume, followed by volume expansion during the interdialytic period.

Peritoneal dialysis has been claimed to provide adequate fluid and sodium removal rates by providing a uniform continuous ultrafiltration. Paniagua et al. correctly emphasized the differences between CAPD and APD: in CAPD patients, the type and the concentration of the osmotic agent used in the dialysis fluids and the permeability of the peritoneal membrane should influence the achievement of an ideal ultrafiltration rate [11,15]. APD has the same effect as CAPD on extracellular fluid volume, although the shorter dwell time could cause higher ultrafiltration volumes; however, the amount of sodium removal is lower mainly because the volume removal is mainly due to an increase in free water removal [16,17]. The study by Paniagua et al. [7] is an important prospective multicenter trial with a great number...
of adult patients (753 patients from 14 different dialysis centers followed for 16 months). The authors reported the role of NT-proBNP as a predictor of mortality due to CVD in dialysis patients, independent of the dialysis modality. Despite the observation of differences in known CVD risk factors between PD and HD patients, to date the results of the few studies available on the influence of dialysis modality on CVD risk are still controversial. A recent paper from Johnson et al. [18] carried out in about 25 000 dialysis patients demonstrates that the risk of death from CVD was significantly increased in PD patients compared to HD patients after the first year of treatment. In contrast, there are different papers that observed no difference between PD and HD patients, for example those carried out by Locatelli et al. [19] in 3120 patients starting renal replacement therapy in Lomardy, Italy, and by Foley et al. [20] in 433 incident dialysis patients. The present study of Paniagua et al. [7] observed that important risk factors for mortality (diabetes, body mass index, nutritional status) are not evenly distributed among the different dialysis modalities. Patients on PD seem to especially have a better outcome in the first period after the beginning of the treatment. We fully agree with the authors that this data could be due to a selection bias in choosing a dialysis modality: students or active workers, for example, choose more frequently APD, a modality allowing better integration in their daily activities. However, in our experience, not only students or active workers are encouraged towards PD. In order to avoid abrupt volume changes, patients with a history of severe cardiac dysfunction are also started on PD, as well as those with severe atherosclerotic vascular disease, in order to preserve their vascular resources as long as possible.

An interesting finding is that the NT-proBNP levels and fluid volume overload preserve their role as markers of mortality, independent from the dialysis modality; this could be due, as also highlighted by Paniagua et al. [7], to other factors influencing fluid volume control such as residual renal function, sodium dietary intake and patient compliance. One of the limitations of this paper [7] is that the authors have relied exclusively on bioimpedance to determine the hydration status of the patients. The lack of cardiac imaging means that some further discussion relating to the dual (and not mutually exclusive) entities of primary fluid overload due to inappropriate desired dry weight or a congestive syndrome secondary to cardiac failure with primary biochemical ‘cardiac distress’ need to be made. One of the major limitations of bioimpedance is that, depending on the timing of measurement, the results can vary substantially, representing an important bias for dry weight assessment. None of the methods for measuring impedance is widely used, probably because of the difficulties in understanding bioimpedance and the lack of any ‘gold standard’ for determining dry weight. The authors tried to overcome this limitation of their study by combining bioimpedance evaluation and blood pressure; the two measurements together may be used to discern if the overhydration is related to positive fluid balance or related to cardiac dysfunction. In the multivariate analysis, both extracellular fluid volume/total body water ratio and systolic blood pressure were independent predictors of mortality.

Conclusions

The paper by Paniagua et al. [7] supports the role of NT-proBNP as a good predictor of mortality in dialysis patients, independent of the dialysis modality and fluid volume overload. Also, the fact that interventions reducing NT-proBNP and fluid volume overload reduce mortality of CKD patients supports the role of these markers as predictors of CKD outcomes.

On the other hand, BNP and its precursor NT-proBNP do not seem to be good markers of effective plasma volume (and intradialytic hypotension) in dialysed CKD patients; they are prevalent markers of left ventricular mass and function.

Considering all these points, further studies are needed with a more homogeneous population (only HD or PD patients or an equal distribution between dialysis modalities) in order to evaluate the real role of NPs as markers of fluid overload and as predictors of mortality in the dialysis population.

Conflict of interest statement. We have had no involvements that might raise the question of bias in the work reported or in the conclusions, implications, or opinions stated.

(See related article by R. Paniagua et al. NT-proBNP, fluid volume overload and dialysis modality are independent predictors of mortality in ESRD patients. Nephrol Dial Transplant 2010; 25: 551–557.)

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Peritonitis continues to plague patients on peritoneal dialysis (PD). A recent paper from the Australian and New Zealand registry showed that infectious mortality over time in PD patients exceeded that seen in haemodialysis (HD) patients [1]. Excluding the first 90 days of dialysis, PD patients had an infectious mortality of 2.8/100 patient-years, compared to 1.7/100 patient-years for HD patients. The relative increased risk of death from infections in PD vs HD developed after 6 months on dialysis and was attributed to peritonitis [1]. The rate of death related to peritonitis was 1.1/100 patient-years or 39% of the total infectious deaths in PD. For a period early in PD (1979–1994) when peritonitis was more frequent than today, peritonitis was a contributor to deaths. A recent paper from the Australian and New Zealand registry showed that infectious mortality over time in PD patients exceeded that seen in haemodialysis (HD) patients [1]. Excluding the first 90 days of dialysis, PD patients had an infectious mortality of 2.8/100 patient-years, compared to 1.7/100 patient-years for HD patients. The relative increased risk of death from infections in PD vs HD developed after 6 months on dialysis and was attributed to peritonitis [1]. The rate of death related to peritonitis was 1.1/100 patient-years or 39% of the total infectious deaths in PD. For a period early in PD (1979–1994) when peritonitis was more frequent than today, peritonitis was a contributor to 16% of all deaths on PD [2]. In a study covering the period from 1986 to 2004, peritonitis-associated mortality was related to organism: 27.5% with fungal, 19.3% with enteric and 15% with *Staphylococcus aureus* peritonitis [3].

*S. aureus* continues to be a serious pathogen in PD patients, causing severe peritonitis and exit-site infections [3,4]. Therefore, targeting methods to reduce *S. aureus* peritonitis is of great interest. Herwaldt and colleagues have demonstrated that, in 95% of patients with nasal and pericatheter colonization, the subtype is the same, as is the ensuing peritonitis [5]. Swartz et al., demonstrated that 85% of those patients presenting with a *S. aureus* peritonitis episode were also culture-positive for the same organism at the exit site [6]. Since the patient is the source of the *S. aureus* causing peritonitis, interest has been focused on decolonization of the patient with *S. aureus*.

Mupirocin prophylaxis has long been proposed as a method for reducing infectious complications due to *S. aureus* in PD patients through decolonization. One of the first and most important studies on this was the multi-centre European trial using intra-nasal mupirocin for the first and most important studies on this was the multi-centre European trial using intra-nasal mupirocin for decolonization of the patient with *S. aureus* causing peritonitis.