Pro-Con Debate

Cardiovascular disease in haemodialysis and peritoneal dialysis: arguments pro haemodialysis

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In end-stage renal disease (ESRD) patients, congestive heart failure (CHF) is a dreadful complication. Its pathogenesis is multifactorial. Chronic arterial hypertension, uraemic cardiomyopathy, coronary artery disease (CAD) and valvular disease all lead to myocardial damage that may eventually result in CHF. Other more or less well-proven contributory factors are chronic volume overload, anaemia, metabolic acidosis, secondary hyperparathyroidism, the malnutrition-inflammation complex syndrome and the haemodialysis (HD) arterio-venous fistula (AVF).

In the Dialysis Outcomes and Practice Patterns Study (DOPPS), the prevalence of CHF in the HD population was reported to be 46% in the US, but only 25% in Europe and as little as 6% in Japan [1]. Such substantial geographical differences may be explained in part by the fact that the US patients were older and had more diabetes, CAD and other vascular diseases than the European and Japanese patients, but they may also derive from different criteria for defining CHF. As a matter of fact, there is a risk of over-diagnosing CHF in ESRD patients who present with oedema, dyspnoea and enlarged heart, due to extracellular volume expansion. Therefore, a wide consensus on the definition of CHF in this setting is mandatory for a more accurate estimation of the magnitude of this phenomenon.

Preventing and treating CHF is a critical task, since nowadays, over 80% of ESRD patients, recently diagnosed with CHF will die within just three years [2].

The topic we wish to debate here is the influence of the initial dialysis modality upon the outcome of patients with ESRD and CHF. In other words, what should we choose for such patients: HD or peritoneal dialysis (PD)? Unfortunately, to answer this dilemma, there is very little evidence to count on. Randomized survival studies are lacking, and for ethical reasons, such studies will probably never be conducted. A single comparative (but still non-randomized) HD vs PD study has been done so far, that specifically addressed the survival of ESRD patients with CHF, namely the one published by Stack et al., in 2003 [3]. Therefore, our discussion also needed to include other studies, comparing the influence of HD and PD upon ‘surrogate’ end points, like CHF risk factors, heart structure and function and risk of developing de novo CHF.

What do we learn from survival studies?

The study of Stack et al.

In a historical US national cohort of over 100,000 incident dialysis patients with a history of CHF, Stack et al. [3] found that the choice of PD was associated with a significantly higher mortality, compared with HD, after two years of therapy. This difference was confirmed in both ‘intent-to-treat’ and ‘as-treated’ analyses. After adjustment for demographics (age, gender and race), baseline comorbidity (hypertension, peripheral vascular and cerebrovascular disease), other variables (body mass index, glomerular filtration rate (GFR), serum albumin and haematocrit) and transplantation rates, in the ‘intent-to-treat’ analysis, the relative risk (RR) of death for PD patients was 1.30 (95% CI = 1.20–1.41) in diabetics and 1.24 (95% CI = 1.14–1.35) in non-diabetics. The mortality risk of CHF patients on PD worsened with time, increasing from 14% during the first 6 months to almost 40% at the end of the observation period in diabetics, and from 11% to 47%, respectively, in non-diabetics. The latter finding suggests that, whatever its mechanisms, PD-associated over-mortality is also a function of time. Furthermore, it was noticed that switching the dialysis modality, independent of the direction of the switch, was associated with a higher mortality. Finally, in patients without CHF, survival rates were independent of dialysis modality in non-diabetics and only slightly
lower in PD-treated than in HD-treated diabetics. Discussing the results, the authors could not provide an evidence-based explanation for the higher risk of death of CHF in patients treated by PD, compared with those treated by HD, but speculated that ultrafiltration (UF) dysfunction, loss of residual renal function (RRF) or other factors, such as accelerated atherosclerosis, increased infection rates or inferior clinical care might have been responsible for the worse outcome of PD patients. It is worth mentioning here that Ganesh et al. [4], studying the same cohort, found that PD was also associated with a higher mortality risk than HD in patients with CAD, both diabetics (RR = 1.23, 95% CI = 1.12–1.34) and non-diabetics (RR = 1.20, 95% CI = 1.10–1.32).

Although the study of Stack et al. [3] was non-randomized, the comparison between HD and PD was remarkably accurate, by adjusting for a large number of covariates and by using both ‘intent-to-treat’ and ‘as-treated’ models, thus reducing the bias resulting from switches in treatment modalities during follow-up. However, besides non-randomization, the study had another important limitation, namely the lack of prospective data on RRF, delivered dose of dialysis, anaemia management, nutritional indices and other clinical indicators that may have varied with treatment modality and time and influenced the survival outcome.

**Other studies**

A few large studies have published comparing the effect of PD and HD on patients’ survival, and still only some of these studies included a stratification of patients into those with and without CHF. Examining data on almost 400,000 US patients (11.6% on PD), followed from dialysis inception up to a maximum of 3 years, Vonesh et al. [5] found that the patients with baseline CHF had similar survival rates on both modalities, except for the subgroup of diabetics aged over 45 years, which had a lower mortality on HD than on PD (RR = 0.80, P < 0.0001). In a recent prospective study involving 1041 incident dialysis patients, Jaar et al. [6] found that, among those with cardiovascular (CV) disease (including CAD, CHF, arrhythmias, cerebrovascular and peripheral vascular disease), the risk of death after 2.4 years of therapy was significantly greater in those undergoing PD than in those undergoing HD, in both an ‘intent-to-treat’ model (RR = 2.10, 95% CI = 1.36–3.25) and a propensity score model (RR = 1.74, 95% CI = 1.15–2.65). On the other hand, there was no difference in survival between PD-treated and HD-treated patients without previous CV disease (RR = 0.83, 95% CI = 0.38–1.81 and RR = 1.11, 95% CI = 0.54–2.26, respectively) [6].

Other large national cohort studies have suggested that special ESRD subpopulations, like the elderly and the diabetics, have a higher mortality rate on PD than on HD [5,7–9]. Assuming that these particular patients have a worse CV status than younger and non-diabetic individuals, one can speculate that HD might do better than PD for patients with CV diseases, including CHF.

**Influence of dialysis modality on CHF risk factors**

There is evidence that, during the first few months or years of therapy, while RRF and diuresis are maintained, PD may provide better fluid and blood pressure (BP) control than HD [10–12], probably thanks to more abundant urine output, continuous UF or better clearance of some hypothetical vasopressor toxins [13]. However, the prevalence of hypertension and overhydration increases after several years on PD, probably as a result of progressive loss of RRF and of peritonealUF capability [14–17]. Peritoneal UF failure is associated with volume expansion, hypertension, left ventricular (LV) hypertrophy and inflammation—all of these being notorious risk factors for mortality, essentially of CV causes [18]. Although the use of icodextrin [19–21] and of more ‘physiological’ biocompatible PD solutions [22] may increase fluid removal, UF failure is still one of the main reasons for ultimate PD technique failure and patients’ transfer to HD.

The mechanisms of AVF-associated heart failure have recently been reviewed by MacRae et al. [23]. They pointed out that patients with high-flow access have volume overload, elevated cardiac output and LV dilution, but whether this leads to overt high-output cardiac failure and over what period of time is unknown. Notably, only a few case reports have been published with high-output heart failure in HD patients and it seems that this is truly a rare condition. As a matter of fact, in a historical cohort study of the United States Renal Data System (USRDS) Wave II Dialysis Morbidity and Mortality Study, Abbott et al. [24] failed to observe any significant differences in the prevalence of CHF between HD patients with a AVF, compared with those using a graft or a temporary catheter as vascular access.

Anaemia is a well-known CV risk factor in both non-renal and ESRD patients. Foley et al. [25] showed that, in dialysis patients, serum haemoglobin levels are inversely correlated with the risk of LV hypertrophy and dilatation: a 1.0 g/dl decrease in serum haemoglobin is associated with a 50% increase in the risk of developing de novo CHF. It has been speculated that better preservation of RRF (including endogenous erythropoietin production), absence of blood loss during HD sessions, better clearance of ‘middle molecules’ or higher efficiency of subcutaneous vs IV erythropoietin explain why PD patients may have less anaemia than their HD counterparts. However, in the US, Snyder et al. [26] recently demonstrated that although PD patients need significantly less amounts of erythropoietin and iron supplements than HD patients, mean serum haemoglobin levels in the two populations, when treated with erythropoietin, are similar.

Lipid disorders are also unanimously recognized risk factors for CAD and CHF, and lipid lowering is recommended by current American College of
Cardiovascular guidelines as a part of the treatment of patients at risk for CHF [27]. Compared with HD patients, PD patients generally have a more atherogenic serum lipid profile, with higher levels of total cholesterol, low density lipoprotein-cholesterol and lipoprotein (a) and lower levels of high density lipoprotein-cholesterol [28]. These abnormalities may be due to peritoneal glucose absorption and loss of proteins in the dialysate (corresponding to a nephrotic-like syndrome). Although still unclear in ESRD patients, we believe that there is little doubt about the negative influence of dyslipidaemia upon CV outcome, given the striking amount of evidence coming from numerous large trials in the general population.

Uraemic toxins have also been involved in CV disease in ESRD patients [29], but exactly which of these substances are cardiotoxic and due to what mechanisms is largely unclear. Advanced glycation end products (AGEs), advanced oxidation protein products (AOPP), homocysteine, phosphate, asymmetric dimethylarginine (ADMA) and cytokines are frequently mentioned as the most likely culprits [30]. There are very few comparative studies between PD and HD, regarding serum concentrations and removal capability of these uraemic toxins and their relation with CV morbidity and mortality. Agalou et al. [31] found higher serum concentrations of glycation-free adducts in PD than in HD patients and in a recent review, Zoccali et al. [32] showed that plasma norepinephrine and ADMA are higher in continuous ambulatory PD (CAPD) than in HD patients, and that these differences are associated with a 16 and 15%, respectively, higher risk of CV events, in multivariate analyses.

Increased arterial stiffness, as a result of arteriosclerosis and arterial calcifications, is characteristic of uraemia and represents an important risk factor for the development of LV hypertrophy and CHF. However, the influence of the mode of dialysis upon this vascular disorder is unclear; in our personal experience, PD patients have stiffer arteries than HD patients [33], although other authors report the opposite [34–36].

Heart changes and the risk of developing CHF during dialysis

Comparative echocardiographic studies between HD and PD patients suggest that heart changes are similar in both populations, provided that fluid status and BP control are also comparable. For example, Gunal et al. [37] found no differences in ultrasound measurements of LV chamber size, wall thickness, LV mass index and ejection fraction between HD and PD patients, when BP levels were equal. Canziani et al. [38] reported a lower prevalence of LV hypertrophy in PD-treated than in HD-treated patients, but BP was also lower in the former [38]. Nevertheless, LV structure and function may worsen in long-lasting PD, if deterioration of RRF and/or peritoneal UF occurs, causing overhydration and hypertension [39–41]. In PD patients, residual GFR is of paramount importance for the heart, as it independently predicts LV mass index [42]. Long-term (76 months) CAPD patients have higher BP and exhibit a higher LV mass index and A/E ratio (a parameter of diastolic function—Doppler derived ratio between the peak atrial filling velocity (A wave) and peak early diastolic flow velocity (E wave) of the left ventricle) and a lower ejection fraction than short-term (28 months) CAPD patients and both long-term and short-term HD patients [43]. Enia et al. [44] compared 51 CAPD with 201 HD patients, on dialysis for 36 and 70 months, respectively, all of them (except eight CAPD patients) virtually anuric. LV hypertrophy was found to be more severe in CAPD patients than in HD patients, and this was clearly in relation with volume overload, since CAPD patients had a higher plasma atrial natriuretic factor, higher left atrial volume and required more anti-hypertensive medication than their HD correspondents [44]. In incident dialysis patients with pre-existing LV dilation, Foley et al. [45] noticed a relentless increase in LV mass index, end-diastolic diameter and cavity volume index over 41 months of renal replacement therapy. PD was associated with significantly lower risk of LV enlargement than HD during the first year of therapy, but not thereafter.

However, the use of hypertonic PD solutions, together with salt intake restriction, can maintain adequate BP control and prevent LV hypertrophy, despite the reduction of RRF, in long-term PD patients [46]. Icodextrin-containing PD solution is a promising alternative, as it was shown to significantly reduce extracellular hydration and LV mass, compared with a standard solution [47]. Should the use of this solution expand, future interesting studies, comparing CAPD patients on icodextrin with well-matched HD individuals, might become feasible.

From all of the above, it results that HD and PD may have different impact on CV risk factors and cardiac structure and function. However, the effect of dialysis modality upon the patients’ risk of developing CHF is unclear, since randomized comparative studies are lacking. In retrospective analyses, Locatelli et al. [48] observed no difference in the 4-year risk of de novo CV disease (comprising CAD and/or CHF) between incident HD and PD patients, after adjustment for age, gender, pre-existing CV disease and diabetic status, while Trespalacios et al. [2] found HD to be associated with significantly greater risk than PD for developing both de novo and recurrent CHF.

Conclusions

A comparison between HD and PD in terms of benefits for ESRD patients with CHF has little evidence-based support, since randomized studies are lacking. Therefore, non-randomized and surrogate end point studies inevitably need to be considered.
Theoretically, PD might have some advantage over HD, in patients with CHF, at least during the first one or two years of therapy, by providing continuous, slow UF, haemodynamic stability and preserving higher urine output, while lacking the AVF-associated hyperkinetic syndrome. However, the advantage of PD is often lost after one or several years, because of progressive peritoneal and renal failure, leading to impaired volume and BP control—major risk factors of cardiac enlargement and dysfunction. Other adverse CV factors, like atherogenic lipid abnormalities, some uraemic toxins accumulation and increased arterial stiffness, may also count as potential drawbacks of PD, compared with HD.

The few outcome studies concerning ESRD patients with CHF and other CV diseases showed that PD, compared with HD, is associated with a significantly higher mortality rate. Other studies suggested that certain ESRD subpopulations, like the elderly and those with diabetes and CAD, also have a longer survival on HD than on PD; as CHF is very likely more prevalent in such patients, these studies might provide indirect evidence that HD is superior to PD when it comes to CHF patients.

Therefore, in our opinion, unless there are compelling indications for PD or contraindications for HD, the latter should probably be recommended as the first option for such patients. Starting on PD and switching to HD when necessary, may also seem a reasonable approach, although, as shown by Stack et al. [3] in the aforementioned study, this strategy is associated with a worsened survival.

Definitely, further survival studies comparing HD-treated with PD-treated ESRD patients with CHF are needed. These studies should use a widely accepted definition of CHF in uraemic patients and include other geographical areas than the US. But, when choosing between PD and HD, there are certainly a multitude of elements to consider, besides the presence or absence of CHF. Patients’ own option and local medical team experience are definitely very important. Whether on PD or HD, careful patient monitoring and aggressive prevention and treatment of CV risk factors, such as overhydration, hypertension, anaemia, dyslipidaemia and inflammation, are critical. It is important to try and avoid peritoneal and renal damage in PD patients, as well as high-flow AVF in HD patients. Expanding the prescription of drugs like angiotensin-converting enzyme inhibitors and β-blockers [49], which seem to be currently underused in this setting [2], and new dialysis technologies, such as icodextrin-based PD-solutions or prolonged HD sessions, may lead to a better outcome of patients with ESRD and CHF, both PD- and HD-treated.

Conflict of interest statement. None declared.

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