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The Influence of Renal Replacement Therapy on Cardiac Disease in the Patient with End-Stage Renal Disease

N. Lameire, H. Hoeben

Cardiac disease exerts a major influence on the morbidity and mortality of patients suffering from end-stage renal disease (ESRD), particularly when treated with dialysis. This paper reviews the distinct impact of each renal replacement therapy, haemodialysis, peritoneal dialysis, and kidney transplantation, on the presence of some cardiovascular risk factors.

The following topics are discussed:

- the prevalence of cardiovascular abnormalities at start and during each analysis modality; among them left ventricular abnormalities, ischaemic heart disease and cardiac arrhythmias
- the evolution of the cardiac abnormalities after renal transplantation
- the risk factors for cardiac disease: hypertension, volume overload, compliance of the great vessels, anaemia, dyslipidaemia, hyperhomocysteinaemia, and hormonal disturbances in female patients

Finally, some therapeutic considerations in the dialysis patients with coronary heart disease are briefly discussed. *J Clin Basic Cardiol 2001; 4: 101–107.*

Key words: dialysis, cardiac disease, transplantation, cardiovascular risk factors

Cardiac disease exerts a major influence on the morbidity and mortality of patients suffering from end-stage renal disease (ESRD), particularly when treated with dialysis. Many recent reviews have demonstrated the frequent occurrence of heart failure and ischaemic heart disease, very high mortality rates, with a high proportion of cardiac deaths in this population [1, 2]. Of deaths classified as cardiac in the United States Renal Data System, cardiac arrest was the attributed cause of death in 39 % of cases, followed by acute myocardial infarction (24 %) [3].

These adverse events can usually be attributed to disorders of cardiac muscle structure and function and/or disorders of cardiac perfusion [4].

The mortality data further suggest that cardiovascular diseases are by far the most common cause of death in haemodialysis, peritoneal dialysis, as well as in renal transplant patients. It is generally accepted that in this population, besides the well-known general risk factors a number of additional uraemia-related cardiovascular risk factors is present [4]. The in-depth discussion of each of these risk factors is beyond the scope of this paper, and recent reviews have been devoted to the many cardiovascular abnormalities in each dialysis modality separately [5, 6].

It is remarkable that the high rate of cardiovascular morbidity and mortality in ESRD patients occurs at a time when the prevalence of coronary artery disease is declining in the general population. This discrepancy is in part due to the demographics of patients about to be started on dialysis: about one-third are diabetic; the average age is now over 60 years with approximately 16 % over 74 years, and many patients have underlying cardiac disease [7].

Among new patients starting dialysis in the USA, 41 % had coronary artery disease and 41 % had heart failure [3].

Although an extensive literature is available on the impact of cardiovascular disease in an end-stage renal disease (ESRD) patient population, very little information is available on the comparative cardiovascular morbidity and mortality of the three major forms of RRT (haemodialysis, peritoneal dialysis, renal transplantation) and on their individual influence on the evolution of these cardiovascular problems.

This paper will attempt to briefly analyse the possible differences in prevalence, morbidity and mortality of cardiovascular diseases in haemodialysis, peritoneal dialysis, and renal transplantation.

The distinct impact of each RRT modality on the presence of some cardiovascular risk factors has been described elsewhere [5, 6]. This paper will focus on studies where comparison between the different dialysis modalities have been analysed.

Comparative Analysis of the Prevalence of Cardiovascular Abnormalities at Start and During Each Dialysis Modality

In the present paper, cardiac disease comprises the disorders of cardiac perfusion, caused by atherosclerotic coronary artery disease or by non-atherosclerotic disease, and disorders of the left ventricular myocardium. The latter includes left ventricular hypertrophy and left ventricular dilatation. All these disorders lead to systolic and diastolic dysfunction and are responsible for heart failure, ischaemic syndromes, arrhythmias and dialysis hypotension.

This analysis will be restricted to studies where the presence of cardiac disease, arterial abnormalities, and arterial hypertension has been directly compared in both dialysis modalities.

Maintenance of normal LV wall stress necessitates the development of LV hypertrophy if LV pressure rises or LV diameter increases. This is initially a beneficial adaptive response [8]. However, continuing LV overload leads to maladaptive myocyte changes and myocyte death, mainly by apoptosis which may be further exacerbated by diminished perfusion, malnutrition, uraemia, and hyperparathyroidism [8, 9]. This loss of myocytes will predispose to LV dilatation and ultimately systolic dysfunction. In addition myocardial fibrosis occurs, which will not only diminish cardiac compliance, but attenuate the hypertrophic response to pressure overload [8].

Disorders of the left ventricular (LV) structure include concentric LV hypertrophy, a response to LV pressure overload, and LV dilatation with hypertrophy, a response to LV volume

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overload [8, 9]. These structural abnormalities predispose to diastolic dysfunction, in which diminished compliance results in a higher than normal change in LV pressure for a given change in LV volume. Ultimately, failure of the pump function of the heart (systolic dysfunction) occurs. Both diastolic and systolic dysfunction predispose to symptomatic left ventricular failure, a frequent occurrence in dialysis patients and a harbinger for early death [10, 11]. In the presence of LV hypertrophy, impairment of coronary perfusion may be catastrophic, resulting not only in regional impairment of LV contraction, but also in LV dilatation and systolic dysfunction [12].

In a Canadian cohort of 432 dialysis patients, followed from the initiation of ESRD therapy, only 16 % had a normal echocardiogram on starting dialysis [13]. 41 % had concentric LV hypertrophy, 28 % LV dilatation, and 16 % had systolic dysfunction. This implies that causes of LV dysfunction are already present in the predialysis phase of chronic renal failure. 275 patients had a follow- up echocardiogram 17 months after starting dialysis therapy [10]. The proportion of those who had a normal echocardiogram was now 13 %, the proportion with concentric LV hypertrophy was 40 %, with LV dilatation 26 %, and systolic dysfunction 20 % [10].

Comparative Studies of Cardiovascular Abnormalities Between Haemodialysis and Peritoneal Dialysis

Peritoneal dialysis and haemodialysis are very different dialysis techniques. Peritoneal dialysis is associated with a lower overall clearance of especially low molecular weight solutes, such as urea and creatinine; however, the clearance with standard peritoneal dialysis (CAPD) is continuous, as opposed to being markedly intermittent in thrice weekly haemodialysis. Peritoneal dialysis is associated with a slower loss of endogenous renal function than in haemodialysis, summarised by Lameire in 1997 [14].

On theoretical grounds, peritoneal dialysis should in contrast with intermittent haemodialysis, have several haemodynamic advantages [15, 16]. Patients undergoing haemodialysis experience rapid changes in solute transport and intercompartimental fluid shifts, with abrupt changes in their volume status. The arteriovenous fistula in haemodialysis patients contributes to a hyperdynamic circulation. Comparatively, the continuous forms of peritoneal dialysis are more gentle to the circulation, with continuous daily removal of solute and fluid. The volume status and blood pressure should thus be better controlled without excess of cardiovascular stress. Since anaemia seems to be a risk factor for cardiac disease in dialysis patients [17], and anaemia is better controlled in peritoneal dialysis patients [18], the negative impact of this factor should be less in peritoneal dialysis.

Left ventricular abnormalities

A recent Canadian analysis has compared the baseline cardiac characteristics in 248 haemodialysis and 185 peritoneal dialysis patients, who were subsequently followed for a mean of 41 months [19]. Compared to haemodialysis patients, peritoneal dialysis patients at start of RRT had a lower incidence of hypertension (20.5 % *vs.* 30.2 %, but a higher incidence of diabetes (34.1 % *vs.* 21.4 %), ischaemic heart disease (27 % *vs.* 18.1 %), and cardiac failure (36.2 % vs. 26.7 %).

The left ventricle echocardiogram was similar as far as mass index and cavity volume were concerned; however, there was a significantly lower fractional shortening. The principal outcomes after approximately 1 year of therapy showed a similar incidence of *de novo* ischaemic heart disease and *de novo* cardiac failure. Both groups of patients showed a similar increase in left ventricle mass index (+23 and +32 g/m^2 in peritoneal dialysis and haemodialysis, respectively) and a similar decrease in fractional shortening. However, whereas the LV cavity volume increased with 5 ml/m^2 in the HD patients, it decreased with 3 ml/m^2 in the PD patients.

There were no differences in the proportion of deaths within the first 2 years of therapy, but after 2 years this proportion was significantly higher in the PD patients (50.7 % *vs.* 35.5 %). Progressive clinical and echocardiographic cardiac disease were not responsible for this late mortality. However, lower mean serum albumin levels in PD patients in the first 2 years of therapy accounted for a large proportion of the increase in subsequent mortality.

An important recent echocardiographic study [20] compared cardiac function in long-term *versus* short-term CAPD and HD patients, respectively. Almost every parameter of LV hypertrophy was significantly more disturbed, and also the incidence of systolic and diastolic dysfunction was higher in the long-term CAPD patients, compared to the three other groups of dialysis patients. It was also suggested that the cause of cardiac dysfunction in long-term PD patients was mainly based on poor blood pressure control, probably due to overhydration.

The decrease in prevalence in cardiovascular risk factors during the first two to three years after the start of dialysis in a CAPD population, followed for 5 years, has also been observed in our unit. At 5 years of CAPD, however, the same prevalence of risk factors, including left ventricular hypertrophy, as before the start was observed [15].

The same Canadian researchers also determined the long-term evolution of cardiomyopathy in dialysis patients in a group of 29 patients (20 HD and 9 PD patients) where four consecutive echocardiograms at yearly intervals were performed [21]. Progressive increases over time in posterior wall thickness, left ventricular end-diastolic diameter, left ventricular mass index, and cavity volume index were observed while mass-to-volume ratios did not change. The most important quantitative changes in mass and volume index occurred between baseline and year 1, although further increases in both parameters were seen after 1 year. Haemodialysis *versus* PD and anaemia were associated with progressive left ventricular enlargement, but only within the first year of dialysis therapy. The left ventricular enlargement seen after one year was independent of anaemia, blood pressure, serum albumin and mode of dialysis. The major reason why progressive LV enlargement took place, especially in the HD patients during the first year, must have been the impact of the A-V fistula. Very large A-V fistulae increase cardiac preload, which is usually offset by increased stroke volume [22], and, according to the Law of Laplace, the short-term trade-off for such an adaptive LV dilation is increased wall tension and oxygen demand. Cardiomegaly with high-output cardiac insufficiency may occur as a complication of high-flow A-V shunts, and cardiac function may return to normal after surgical correction [23].

In contrast, in PD the impact of intraperitoneal infusion volume on cardiac function should be mentioned. A significant decrease in left ventricular internal dimensions in diastole from the infusion of 3 litres or more of dialysate has been observed. This was correlated with the rise in intra-abdominal pressure. These effects were confined to the subgroup of patients with increased left ventricular wall thickness. Infusion of 1 or 2 litres did not affect systolic function.

Ischaemic heart disease

Coronary artery disease is the usual cause of symptoms of ischaemic heart disease in dialysis patients [24]. On starting dialysis, ischaemic heart disease is present in 22 % [13]. 73 %

of patients with symptoms of ischaemic heart disease have coronary artery disease [24]. However, non-atherosclerotic disease, resulting from small vessel disease, and/or from the underlying cardiomyopathy, may account for a substantial minority (27 %) of cases of symptomatic ischaemic heart disease [12, 24]. Multiple factors contribute to the vascular pathology of chronic uraemia, including chronic injury to the vessel wall, prothrombotic factors, lipoprotein interactions, proliferation of smooth muscle cells, increased oxidant stress, diminished antioxidant stress, hyperhomocysteinaemia, hypertension, diabetes and smoking [8].

In a large cohort (n = 496) of new Canadian haemodialysis patients who were followed for a mean of 218 days, there were 30 ischaemic events (myocardial infarction or angina) requiring hospitalisation, giving a probability of 8 % per year, and there were 40 episodes of pulmonary oedema requiring hospitalisation or additional ultrafiltration, giving a probability of 10 % per year [25].

Out of a group of 31 PD patients only 15 had no evidence of ischaemic heart disease [26]. *De novo* appearance of ischaemic heart disease in CAPD patients has been reported to be 8.8 % after one year and 15 % after 2 years [27].

As mentioned before, a lower incidence of ischaemic heart disease was present at baseline in PD patients compared to HD patients in the recent large Canadian study [19]. However, after one year of dialysis the prevalence of *de novo* ischaemic heart disease was similar in both dialysis groups (14.1 % in PD and 10.3 % in HD).

Accompanying the high cardiovascular mortality are the high rates of acute clinical events, including myocardial infarctions, cerebrovascular incidents and sudden death in an ESRD population. In addition, there is a marked increase in mortality after an acute cardiovascular event. Survival analysis of patients from the United States Renal Data System coded with a first myocardial infarction occurring between 1977 and 1985 suggested that the overall mortality was 59 % in the first year following the index infarction, 73 % at 2 years, and 90 % at 5 years [28]. For comparison, during this time period the 1 year mortality rate following acute myocardial infarction in the general population was approximately one-half the mortality rate seen in the US renal cohort.

Cardiac arrhythmias

In patients without renal failure, left ventricular hypertrophy and coronary heart disease appear to be associated with an increased risk of arrhythmias. As outlined above, these cardiac diseases are among the most prevalent in ESRD patients. In addition, serum electrolyte levels that can affect cardiac conduction, including potassium, calcium, magnesium, and hydrogen are often abnormal or undergo rapid fluctuations during intermittent haemodialysis. For all these reasons, cardiac arrhythmias should be common in these patients. The presence of all these confounding factors explains why the assessment and interpretation of arrhythmias in haemodialysis patients is difficult.

Peritoneal dialysis: Holter monitoring of cardiac rhythm of 21 CAPD patients revealed a high frequency of atrial and/or ventricular premature beats [29].

There were no differences in the type and frequency of the extrasystoles between the day on CAPD or the day on which dialysis was deliberately withheld. It seems thus that in contrast with haemodialysis, CAPD is by itself not responsible for provoking or aggravating arrhythmias.

A recent study in which 27 CAPD patients were compared with 27 HD patients revealed that severe cardiac arrhythmias occurred in only 4 % of CAPD and in 33 % of the HD group [30]. Patients in both groups were matched for age, sex, duration of treatment, and aetiology of chronic renal failure. The lower frequency of left ventricular hypertrophy, the maintenance of a relatively stable blood pressure, the absence of sudden hypotensive events, and the significantly lower incidence of severe hyperkalaemia in patients on peritoneal dialysis may be the explanation of this difference [31].

Evolution of the Cardiac Abnormalities After Renal Transplantation

It should be realised that patients who undergo renal transplantation belong in general to a selected subgroup of the dialysis population. Although in many transplant centres the selection criteria are nowadays becoming less stringent, patients offered transplantation are on average younger and have little or at least a treated cardiac comorbidity. Despite this, cardiovascular disease is the most common cause of death after renal transplantation in the USA, according to the 1994 USRD data In the Canadian echocardiographic study, only 11 % of the subgroup of dialysis patients who were transplanted had previous heart failure and 1 % had myocardial infarction [32]. Nonetheless, many of them had abnormal LV structure and/or function before transplantation. After transplantation, LV mass index regressed in those with concentric LV hypertrophy. Both LV mass index and LV volume improved in those with LV dilatation. However, in many patients LV structure did not normalise. All 12 patients with systolic dysfunction (fractional shortening of < 25 %) normalised [32].

A recent analysis [33] described LV hypertrophy to be present in 64–70 % of men and in 63–65 % of women at the time of transplantation. Both end-diastolic and systolic diameters were increased and 83 % of the patients suffered from ventricular dilatation. It appeared that despite the potential benefits of transplantation on cardiac function, left ventricular hypertrophy, ventricular dilation and systolic dysfunction were all associated with adverse outcome following transplantation. At least in this study, the echocardiographic findings identified markers for premature deaths.

Ischaemic heart disease remains, however, the most frequent cardiac complication after renal transplantation. Kasiske et al. [34] calculated by actuarial analysis that 23 % of patients who survived with a functioning allograft for 15 years developed ischaemic heart disease.

Among the most significant risk factors figured age, male sex, diabetes mellitus, acute rejection, hyperlipidaemia, and the presence of pretransplant ischaemic heart disease.

In Canada, the prevalence of ischaemic heart disease is about 15 % in renal transplantation. As risk factors for coronary artery disease were mentioned: hypertension, diabetes, hyperlipidaemia, smoking, prothrombotic factors and LV hypertrophy [35].

A recent report from Düsseldorf University Hospital described the development of atherosclerotic cardiovascular diseases in 11.7 % of 427 transplant patients. Coronary artery disease was the most common with a frequency of 9.8 % [36]. Similar risk factors were noted as described above.

Risk Factors for Cardiac Disease

The risk factors can be categorised as haemodynamic, metabolic, or other. Circumstantial evidence and longitudinal studies support several risk factors as important for the development of cardiac disease, but there are no clinical trials which have demonstrated that any risk factor intervention leads to clinical benefit in dialysis patients.

Besides the risk factors present at the onset of dialysis, we will only discuss briefly hypertension and some metabolic

risk factors which may be differently influenced by the several RRT modalities.

Hypertension

In a longitudinal study, the importance of raised systolic blood pressure in the development of LV hypertrophy was shown [37] and the independent association of hypertension with concentric LV hypertrophy, has been reported in dialysis patients [38].

Hypertension is a common finding in dialysis patients. Approximately 80 % of patients are hypertensive at the initiation of dialysis. However, in haemodialysis the prevalence falls to 25 to 30 % by the end of the first year, due largely to volume control [39].

Although CAPD has some theoretical haemodynamic advantages over haemodialysis because of the absence of an arteriovenous fistula contributing to a hypercirculatory state, and the avoidance of intermittent and abrupt changes in volaemia, the prevalence of hypertension in a recent large Italian multicentre population of 504 peritoneal dialysis patients was 88 % [40]. This study clearly demonstrates that hypertension also in a peritoneal dialysis population is an unsolved problem.

Saldanha and colleagues [41] recently followed the time sequence of changes in blood pressure, body weight and haematocrit in 2 groups of CAPD patients. The first group of patients was transferred from HD to CAPD while the second group was treated with CAPD as initial dialysis mode. The patients coming from HD manifested a progressive fall in blood pressure in the first months after they were transferred to CAPD. An approximately similar, but less important fall in blood pressure was observed in the new CAPD patients during the first 2 years of their dialysis treatment. Whereas approximately 60 % of the HD patients did not need antihypertensive therapy, this decreased to 40 % after the transfer to CAPD. This effect was transient as the number of patients who needed more antihypertensive drug treatment subsequently increased with time. In the new CAPD patients, there was an initial increase in patients who did not need antihypertensive drug therapy but as in the first group, the patients who needed more drug therapy became larger with time. Also in our long-term study comprising 23 CAPD patients followed for at least seven years, no significant changes in blood pressure were found, but an increased requirement for antihypertensive medication was observed [42]. This has recently been confirmed by Amann et al. [43]. It seems thus that the blood pressure can be readily controlled in CAPD patients during the first 2 to 3 years of dialysis but once the residual renal function is very low or absent, the control becomes more difficult and the patients need a higher number of antihypertensive drugs.

It has been widely held that hypertension is a major cause of mortality in dialysis patients. In the widely quoted study of Charra et al. [44, 45], haemodialysis patients received very large doses of dialysis, with a mean achieved KT/V urea of 1.67; the 5-year survival of these patients was an unheard-of 87 %. In this study, 98 % of patients achieved normotension without the need for antihypertensive agents. The authors speculate that lack of hypertension or toxic antihypertensive drugs due to a careful restriction of the dietary sodium intake, together with a thrice weekly, slow dialysis of 8 hours per dialysis session resulting in a perfect volume control accounted for much of the excellent survival achieved in their study.

In the Canadian cohort, mean arterial blood pressure levels were 101 ± 11 mmHg [38]. An inverse relationship between blood pressure levels and mortality was observed, with an (adjusted) increase in mortality of 22 % for each 10 mmHg decrease in the mean arterial blood pressure distribution curve. Conversely, even within this range, rising blood pressure was independently associated with an increase in LV mass index and cavity volume on follow-up echocardiography, *de novo* ischaemic heart disease, and *de novo* cardiac failure. Paradoxically, Zager et al. reported in haemodialysis patients a "U" curve association between blood pressure and mortality, suggesting that hypotension might be as "dangerous" as hypertension in this setting [46, 47]. However, hypotension, especially at the start of dialysis, is a marker of severe underlying disease, mostly congestive heart failure [38]. These results probably reflect more that it is the underlying disease and not the hypotension by itself that causes the mortality. We therefore believe that it would be dangerous to conclude from these results that the current recommendations for the treatment of hypertension in dialysis patients should be changed.

A blunted circadian blood pressure difference is associated with an increased incidence of left ventricular hypertrophy in essential hypertension [48], and hence could lead to more cardiovascular complications. The influence of variations in fluid state on diurnal blood pressure has been studied in normotensive and hypertensive HD, PD and control patients [49]. Although in most patients a day-night blood pressure difference could be demonstrated, the responses were blunted in the dialysis patients when compared with the controls, but no significant differences between HD and PD patients were found. The conclusion of the study was that factors other than changes in extracellular volume are responsible for the blunted day-night difference in blood pressure. In contrast, Rodby et al. [50] found that HD had significantly higher systolic blood pressures and higher "systolic loads" (higher percent systolic values > 140 mmHg) than PD patients.

It is of interest to note that the abnormal blood pressure diurnal rhythm is not modulated by successful renal transplantation [51]. It should also be mentioned here that the prevalence of posttransplant hypertension severe enough to require treatment was about 50 % in the pre-cyclosporine era, but has increased to about 80 % since cyclosporine has been routinely used as an essential immunosuppressive drug [33–36].

Volume overload

As outlined elsewhere [6], the LV diastolic diameter is increased in dialysis patients. The changes are moderate, the values usually lying around the normal upper limits, but true LV dilatation is observed in 32 % to 38 % of patients. The ventricular enlargement is probably attributable to chronic volume/flow overload and high-output state, associated with three factors: (1) salt and water retention; (2) anaemia and (3) arteriovenous shunts, the latter obviously in HD patients.

Defining 'euvolaemia' in HD patients is a dilemma because of the constant dysvolaemia caused by rapid fluid withdrawal during dialysis and the unpredictable and uncontrollable fluid and salt intake by the patient in the interdialytic interval. It is recognised that intradialytic complications, among them intradialytic hypotension, are influenced by the balance between ultrafiltration rates and plasma refilling, which is largely dependent on hydration of the interstitial space [52, 53].

It is well accepted that keeping the blood pressure normal in haemodialysis patients requires full attention to control of the dry weight [54–56]. However, correct estimation of the dry weight in a haemodialysis patient is with clinical or technical means difficult to do [57].

It is believed that peritoneal dialysis, because it is a continuous process, is better at controlling salt and water overload than haemodialysis. However many CAPD patients are actually fluid overloaded [58]. Some haemodynamic studies performed at the moment of renal transplantation of CAPD patients show that they are constantly overhydrated [58]. The overhydration is further demonstrable when CAPD patients are transferred to HD [14]. Because the transperitoneal ultrafiltration is dependent on osmotic – induced flow due to the presence of glucose as osmotic agent in the dialysis fluid, both the presence of a hyperpermeable peritoneal membrane leading to high peritoneal glucose transport with rapid dissipation of the osmotic gradient resulting in insufficient peritoneal ultrafiltration and the disappearance of the residual renal function contribute to the volume overload and cardiovascular outcome of the PD patient. Both phenomena may occur after some years on peritoneal dialysis [14, 59].

Compliance of the great vessels

Besides atherosclerosis, characterised by the presence of plaques, and altering primarily the conduit function of the arteries, the spectrum of arterial alterations in ESRD patients also includes non-atheromatous remodelling of the vascular wall. The latter type of remodelling alters the damping function of the arteries and is associated with a haemodynamic burden whose consequences are different from those attributed to plaques [60, 61].

From normal cardiovascular physiology it is known that there is a pulse wave propagated from the left ventricle through the aorta and arterial vessels following each systolic contraction. The velocity of this pulse wave is directly related to the distensibility of the arterial wall. The more compliant the artery, the slower the velocity of the pulse wave. In a recent study by Blacher et al. [62], stiffness of the carotid artery was found to be an independent predictor of all-cause and cardiovascular mortality in haemodialysis patients. This implies that physical changes in the vascular wall occur as patients progress to ESRD and these changes may be present before the initiation of renal replacement therapy. In addition to arterial calcification due to hyperphosphataemia and hyperparathyroidism, other remodelling factors of the arterial wall may be important. The volume overload of renal patients leads to increased tensile stress acting against the arterial wall. As a result, the dynamic vascular wall undergoes remodelling events which result in hypertrophy of the surrounding media and smooth muscle. This hypertrophied vessel is then rendered less compliant.

Anaemia

In ESRD patients, an association between LV dilatation and anaemia has been observed. After adjusting for age, diabetes, ischaemic heart disease, blood pressure, and serum albumin levels, each 10 g/L decrease in mean haemoglobin level was independently associated with the presence of LV dilatation (odds ratio: 1.46 for each 10 g/L decrease) [63]. Anaemia was independently associated with the development of *de novo* cardiac failure, as well as overall mortality. The time to onset of heart failure according to the level of haemoglobin up to development of heart failure or final follow-up was more readily apparent in HD than in PD patients, possibly because the latter group had higher mean haemoglobin levels while on dialysis therapy [63].

As discussed in [6], several studies have examined the effect of partial or complete correction of anaemia with recombinant erythropoïetin (rHuEpo) on echocardiographic abnormalities. Most of these have had small numbers of patients, and have been before-after surveys, without a control group. In spite of these limitations, the studies have consistently shown that treating anaemia leads to a decrease in hypoxic vasodilatation, an increased peripheral resistance, reduced cardiac output, and partial reversal of LV dilatation and hypertrophy. In general, fewer PD than HD patients require rHuEpo treatment to control their anaemia, and PD patients who receive rHuEpo use approximately 30 % less drug than do their HD colleagues [64].

The ideal target of haematocrit or haemoglobin to achieve in dialysis patients is currently under discussion. A recent study by Besarab et al. [65] described a higher rate of cardiac deaths in HD patients with clinical evidence of congestive heart failure or ischaemic heart disease when their haematocrit was raised to the normal level of 42 % with rHuEpo. However, these results were not confirmed by Locatelli et al. [66], and the American study was criticised on methodological grounds [67].

Dyslipidaemia

In uraemia, dyslipidaemia is common but it is different in HD and PD patients [68]. PD is associated with a more atherogenic lipid profile. Total and LDL cholesterol are elevated in 20 %–40 % of patients and 25 %–50 % of patients have hypertriglyceridaemia and low HDL levels. In general these abnormalities are slightly less frequent in HD. Lp(a) is also increased to a greater percentage in PD than in HD patients [69, 70]. Part of the more pronounced dyslipidaemia in PD may be related to the continuous glucose uptake across the peritoneal membrane or to the in general lower plasma albumin levels in these patients [15, 68].

Hyperhomocysteinaemia

This abnormality is common in patients with end-stage renal disease and may contribute to the development of atherosclerosis and thromboembolic vascular disease in these patients [6].

A recent study [71] observed significantly higher plasma homocysteine concentrations and lower plasma folate levels in HD patients compared to PD patients.

The role of oxidative stress in uraemia and its impact on cardiac disease in dialysis has been recently reviewed in-depth elsewhere [72]. It is sufficient to say here that the changes observed in the indicators of oxidative stress generally apply to both HD and PD.

Hormonal disturbances in female patients

Chronic renal failure in women is frequently accompanied by endocrine disturbances leading to menstrual and fertility disorders. The postulated cause for these abnormalities appears to be a defect in the hypothalamic regulation of gonadotrophin secretion resulting in lower estradiol peaks, lower follicle stimulating hormone (FSH)/luteinizing hormone (LH) ratios and higher prolactin concentrations. These hormonal disturbances resemble the post-menopausal state which is characterised by an excessive cardiovascular morbidity and mortality. It is well known that in postmenopausal women with normal renal function, estrogen replacement therapy decreases cardiovascular mortality by 50 %, in part because of the beneficial effects on the lipoprotein profile. Recently, hormone replacement therapy in 11 postmenopausal women with ESRD significantly increased HDL cholesterol to an extent that would be expected to be associated with an improved cardiovascular risk profile [73].

However, estrogen therapy in postmenopausal women has not only several beneficial effects but serious risks as well. Since there are at present no long-term studies with hormonal replacement therapy in uraemic women on haemodialy-

sis or peritoneal dialysis available, it is difficult to recommend such therapy to all female dialysis patients.

Other risk factors

Other known risk factors for cardiac disease in dialysis patients include hyperparathyroidism and disturbances in the calcium-phosphorus metabolism, biocompatibility of dialysis membranes, and systemic inflammation. In this regard it is interesting to note that CRP levels are frequently elevated in ESRD patients, particularly in HD patients [74]. However, CRP levels in PD patients are also predictors of death [75].

Therapeutic Considerations in the Dialysis Patient with Coronary Heart Disease

The accurate identification and treatment of myocardial ischaemia can be difficult in dialysis patients. In these preload-sensitive patients with a high prevalence of left ventricular hypertrophy and attendant abnormalities of left ventricular diastolic dysfunction, the symptoms of volume overload and flow-limiting coronary artery obstruction may be identical. Particularly in diabetic patients the recognition of ischaemic heart disease is difficult because these patients are often asymptomatic because of autonomic denervation. Since many of the non-invasive indices of coronary artery disease such as myoglobin, cardiac troponin T and I isoforms, transient ST segment depression on ambulatory electrocardiography, baseline or exercise electrocardiogram, thallium scan, and dobutamine stress echocardiography and others are far from reliable, there is almost no alternative to coronarography to exclude ischaemic heart disease in the patient on dialysis. When evolving myocardial infarction is suspected, thrombolysis and/or PTCA is indicated. Preliminary data suggest a striking under-utilisation of thrombolytic therapy in dialysis patients with acute myocardial infarction. In these patients thrombolytic therapy showed a 28 % reduction in all-cause death risk [76].

This underutilisation of thrombolysis may reflect both the difficulty of timely recognition of AMI due to "atypical " presentation and the fear of haemorrhagic complications. However, the treatment of ESRD patients with AMI should employ strategies utilised in non-ESRD patients, including aspirin, anticoagulants, beta-blockers, and angiotensin-converting enzyme inhibitors.

Choosing the optimal method of coronary revascularisation is a difficult problem in dialysis patients. Clinical outcome data on the results of coronary revascularisation in dialysis patients have reported on small retrospective series, and none have been encouraging regarding the long-term of PTCA. Particularly the restenosis rate after PTCA is much higher in ESRD patients compared to non-uraemic patients. Based on an analysis of the USRDS database, it was concluded that outcome is superior when dialysis patients are treated with bypass surgery when compared to PTCA with regard to the end-points overall death, cardiac death, and combined cardiac end-points. The more beneficial effects of CABG when compared to PTCA were particularly present in the diabetic population [77].

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