The beneficial effects of intervention in early renal disease

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Abstract

In renal disease, anaemia is a risk factor for cardiovascular disease (CVD), such as left ventricular hypertrophy (LVH), in both dialysis patients and patients with early renal disease. During the past decade, many studies have showed that partial correction of anaemia leads to partial regression of LVH in hypertensive and normotensive dialysis patients. Several reports support the pre-dialysis use of epoetin. Evidence of cardiovascular risk reduction with epoetin treatment in pre-dialysis patients is growing. For example, in an open, prospective study of epoetin in pre-dialysis patients, an increase in mean haemoglobin of 2.7 g/dl was accompanied by a decrease in left ventricular mass index in almost all patients. This regression, obtained in the absence of improved blood pressure (BP) control, confirms the role of anaemia in the genesis of LVH. These results have been confirmed in two recent studies. Risk reduction strategies (i.e. BP control, lipid lowering, smoking cessation, anaemia correction) from the earliest stages of renal disease may facilitate the prevention of cardiovascular conditions such as LVH in chronic renal failure (CRF) patients. Indeed, if all the well recognized risk factors (including anaemia) are aggressively identified and treated, then long-term reductions in cardiovascular morbidity and mortality should be achieved. In conclusion, preliminary studies show reversal of hypertrophy after correction of renal anaemia with epoetin. Extrapolation of results from studies in CRF suggests the use of earlier treatment of anaemia to maximize cardiovascular benefits. Further studies of the cardiovascular benefits of earlier epoetin intervention in early renal disease are indicated.

Keywords: anaemia; epoetin; left ventricular hypertrophy; pre-dialysis; progressive renal insufficiency

Anaemia—a cardiovascular risk factor in ESRD patients on dialysis

In end-stage renal disease (ESRD) patients on dialysis, in addition to ‘traditional’ risk factors for cardiovascular disease (CVD) such as advanced age and hypertension, uraemia-specific factors such as anaemia are also important [1,2]. Indeed, the importance of anaemia in ESRD dialysis patients was shown by the observation that a decrease in haemoglobin (Hb) level of 1 g/dl incrementally increased the risk of mortality by 18–25% and of left ventricular hypertrophy (LVH) by ~50% [1]. More recently, a retrospective study of almost 100 000 dialysis patients showed that improved survival was associated with sustained increases in haematocrit (Hct) levels [3]. Furthermore, in a prospective study of >50 000 dialysis patients on the Lombardy Dialysis Registry in Italy, epoetin therapy was associated with a 30% reduction in the crude relative risk of mortality [4].

Anaemia—a cardiovascular risk factor in early renal disease

A growing body of evidence also supports the role of anaemia as a cardiac risk factor from the early (pre-dialysis) stages of renal disease. In pre-dialysis chronic renal failure (CRF) patients, anaemia has been shown to correlate with left ventricular growth: a 0.5 g/dl decrease in Hb level was associated with a 32% increase in the risk of left ventricular growth in a Canadian cohort of pre-dialysis patients with renal insufficiency [5]. Although a decreased Hb level appears to put patients at increased risk of cardiovascular complications, it remains to be determined whether complete or partial anaemia correction in the earlier stages of CRF leads to a reduction in cardiovascular morbidity or mortality [2].

LVH in renal disease

LVH is an important CVD risk factor in renal disease. LVH is not only a consequence of volume and pressure...
overload, but is an important independent risk factor. LVH has a high prevalence in ESRD patients: \( \sim 75\% \) of incident dialysis patients present with LVH [6]. However, LVH is also prevalent (25–50\%) in the early stages of CRF [5,7]. Indeed, left ventricular growth itself is a strong, independent predictor of lower survival rates, cardiovascular mortality, arrhythmias and sudden death [8]. Importantly, left ventricular growth is modifiable via the treatment of hypertension and anaemia.

**Effect of anaemia correction on LVH in dialysis patients**

In the past decade, several studies have demonstrated that partial correction of anaemia leads to partial regression of LVH in patients undergoing dialysis [9–11]. Reduction of LVH has also been demonstrated in a study of normotensive dialysis patients [12]. However, ventricular mass did not reach normal values in any of these studies. Possible reasons why only partial regression was obtained include: (i) the multifactorial origin of LVH (i.e. only partial treatment of the condition); (ii) incomplete anaemia correction (i.e. insufficient treatment); and (iii) the presence of myocardial fibrosis (i.e. delayed treatment, too late to achieve complete regression).

The improvement in LVH and cardiac performance associated with anaemia correction with epoetin has also been confirmed in recent studies in dialysis patients [13,14]. However, the multifactorial pathogenesis of LVH was highlighted in the study of Massimetti et al. [13]. In this study, for patients with similar severity of anaemia, decreases in left ventricular mass index (LVMI) associated with anaemia correction were observed only in those patients with significant hypertrophy at the onset of therapy. Furthermore, in the study of Jeren-Strujic et al. [14], despite a 35\% increase in Hb level, epoetin therapy again produced only partial morphological regression of pre-existing LVH.

Therefore, since normalization of LVH cannot be achieved at this late stage for dialysis patients, the question arises as to whether early intervention with epoetin would yield greater benefits.

**Early anaemia correction in pre-dialysis patients**

There have been several reports supporting the pre-dialysis use of epoetin [15–18]. The most recent of them, a 1-year study by Albertazzi et al. [15], used a low-dose protocol and a Hb target level of 10–11 g/dl. Anaemia was effectively corrected without changing the rate of decline of renal function or the mean blood pressure (BP).

In 1999, the European Best Practice Guidelines for the Management of Anaemia in Patients with CRF were published [19]. Guideline 4 recommends consideration of epoetin use when the Hb level is <11 g/dl and other possible causes of anaemia have been excluded, and states that ‘this applies equally to patients with CRF on dialysis and to those not yet receiving dialysis’. However, evidence of the added cardiovascular complications and the benefits of aggressive anaemia treatment for pre-dialysis patients has only recently come to light.

**Cardiovascular benefits of early intervention**

In 1997, an open, prospective study examined cardiovascular changes after epoetin treatment in 11 pre-dialysis patients [20]. The main question investigated by this study was whether epoetin treatment can induce changes in ventricular function and structure without worsening of BP or changes in the rate of progression of renal insufficiency. In this study, anaemia was successfully corrected after 3 months of treatment. Hb level increased from 9 to 11.6 g/dl after 3 months and was maintained at this level for a further 3 months (Figure 1).

Echocardiographic measurements showed that cardiac output had decreased significantly after 3 months of treatment; this reduction was maintained at the 6-month time-point. The accompanying decrease in ventricular mass required more time to occur and so the reduction in LVMII reached significance only after 6 months of treatment (Figure 1). Thus, functional cardiac changes preceded structural changes. Importantly, analysis of the reciprocal serum creatinine concentration vs time curve in these patients showed no significant changes in the rate of CRF progression with epoetin therapy. Furthermore, there were no significant changes in mean BP in these patients.

Therefore, the main findings of this study were that epoetin partially corrected anaemia (Hb level 11.7 g/dl after 6 months) without adversely affecting renal function and with no major changes in 24-h BP profiles. In addition to early functional changes in

![Fig. 1. Haematocrit levels at baseline and after 3 and 6 months of epoetin therapy superimposed on cardiac output changes and regression of LVH (adapted from Portoles et al. [20]).](image)
cardiac output, mean LVMI decreased from ~180 to ~150 g/m². Therefore, the increase in mean Hb level of almost 3 g/dl in these patients was paralleled by a decrease in LVMI in almost all patients (Figure 2). This regression, obtained in the absence of improved BP control, confirms the role of anaemia in the genesis of LVH and opens up new therapeutic possibilities in pre-dialysis patients.

Many of the benefits of epoetin in dialysis patients (e.g. anaemia correction and improvements in cognitive function, exercise tolerance, quality of life. LVH and mortality risk) [3,4,9,12,21–25] are now also being demonstrated in the pre-dialysis phase (anaemia correction and improvements in cognitive function, exercise tolerance, quality of life) [26–30]. In addition, evidence of cardiovascular risk reduction with epoetin treatment in pre-dialysis patients is growing. For example, in a study of nine pre-dialysis CRF patients treated with epoetin, while partial correction of Hct (32%) after 4 months was associated with a trend towards a reduction in LVMI, normalization of Hct (39%) at 12 months was associated with a significant reduction in LVMI [31] (Figure 3). Moreover, 24-h BP control and renal function decline were not adversely affected by the normalization of Hct. The authors concluded that, with regard to LVH regression, normalization of Hct with epoetin treatment during the pre-dialysis period was more effective than partial correction of anaemia.

Another very recent study in 102 anemic pre-dialysis patients confirms the partial regression of LVMI (from 171 to 165 g/m²) in patients with basal LVH after partial correction of anaemia (Hb rises from 9 to 11 g/dl) with epoetin. Patients with basal LVH, but without epoetin, show no change in LVMI after 6 months, with similar Hb levels [32]. However, perhaps even more promising was the observation in patients without basal LVH that LVMI remained stable during epoetin therapy but increased in the absence of epoetin. These results were achieved without changes in mean BP or antihypertensive therapy, and suggest that early anaemia correction may even protect against the development of hypertrophy in patients with anaemia.

Therefore, risk reduction strategies (i.e. BP control, lipid lowering, smoking cessation, anaemia correction) are proposed from the earliest stages of renal disease, when the patient’s heart is normal or has minimal hypertrophy. This approach may offer the opportunity to prevent the development of cardiovascular conditions such as LVH in patients with CRF. Indeed, if all the well recognized risk factors, including anaemia, are aggressively identified and treated, then long-term reductions in cardiovascular morbidity and mortality should be achieved.

**Conclusion**

In summary, anaemia is a risk factor for LVH and increased mortality. Preliminary studies show reversal of hypertrophy after correction of renal anaemia with epoetin. Extrapolation of results from studies in CRF suggests earlier use of treatment of anaemia to maximize cardiovascular benefits. Therefore, it is now essential that further studies of the cardiovascular benefits of earlier epoetin intervention in early renal disease are conducted.

**References**

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