

## **Pathophysiology of cardiovascular damage in the early renal population**

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### **Abstract**

In renal disease, mechanisms available to compensate for the reduced haemoglobin levels associated with anaemia include increased oxygen extraction from peripheral tissues and, primarily, increased blood flow and changes in blood flow distribution. Haemodynamic changes induced by anaemia include decreases in blood viscosity, peripheral vascular resistance and oxygen delivery, and an increase in sympathetic activity. The overall effect of anaemia is a chronic increase in cardiac output and cardiac work. Under normal conditions, the increased cardiac work and blood flow associated with anaemia results in adaptive left ventricular hypertrophy (LVH)/remodelling and adaptive arterial hypertrophy/remodelling. However, under uraemic conditions these changes lead to maladaptive hypertrophy and arteriosclerosis. In end-stage renal disease (ESRD) patients, increases in both left ventricular end-diastolic volume and mass are related to decreases in haemoglobin. Therefore, LVH progresses in parallel with changes in haemoglobin level and is associated with decreased survival in ESRD patients receiving renal replacement therapy. In conclusion, anaemia is a contributory factor to LVH in renal disease and cardiovascular damage starts at an early stage. Therefore, early intervention to treat anaemia in these patients can prevent or delay this damage.

**Keywords:** anaemia; cardiovascular remodelling; left ventricular hypertrophy; renal disease; uraemia

### **Compensatory mechanisms in response to reduced haemoglobin concentrations**

The delivery of oxygen to tissues is influenced by three main factors: haemoglobin (Hb) concentration

(oxygen-carrying capacity of blood), adaptation of peripheral tissue and affinity of Hb for oxygen, and blood flow. A consequence of anaemia in renal disease is decreased Hb concentration. Under these circumstances, two mechanisms are still available to compensate for this reduction in oxygen delivery.

The first mechanism is increased oxygen extraction by the peripheral tissues. This is achieved via a reduction in the affinity between Hb and oxygen. An example of this mechanism is the shift of the Hb–oxygen dissociation curve to the right due to increased 2,3-diphosphoglycerate levels or acidosis [1]. However, this mechanism is limited in effect, perhaps compensating for a fall in Hb level of no more than 1–2 g/dl.

The primary mechanism compensating for decreases in Hb level is increased blood flow coupled with blood flow redistribution. These haemodynamic changes are complex and involve several mechanisms, some related to rheological effects and others related to hypoxia-induced vascular effects. These mechanisms, which lead to increased cardiac output as the result of decreased blood viscosity and decreased peripheral vascular resistance [2], are summarized in Figure 1. A decrease in blood viscosity enhances venous return; this in turn increases pre-load and left ventricular filling, which results in increased cardiac output. At the same time, decreased oxygen delivery leads to arterial vasodilation. Mechanisms involved in this vasodilation include 'hypoxic vasodilation' mediated via the production of various hypoxia-generated metabolites, increased availability of nitric oxide, and, in chronic anaemia, angiogenesis via the opening of new capillaries [3]. Arterial vasodilation also reduces peripheral vascular resistance and increases cardiac output. Finally, decreased oxygen delivery also increases sympathetic activity. This also leads to increased cardiac output via either an increase in myocardial contractility or an increased venous return secondary to increased venous tone. Therefore, the overall effect of anaemia is a chronic increase in cardiac output and cardiac work, which leads to left ventricular hypertrophy (LVH).

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**Pressure and volume overload—effects on left ventricular structure and function**

Changes in left ventricular structure and function occur as a result of both volume overload and pressure overload [2]. Volume overload is related to arteriovenous fistula, sodium/water retention and anaemia, the latter being associated with increased stroke volume and increased heart rate [4]. In pre-dialysis chronic renal failure patients, chronic anaemia is probably the most important factor in volume overload, as arteriovenous fistula and sodium/water retention are absent. In end-stage renal disease (ESRD) patients, volume overload usually also occurs in parallel with pressure overload. Causes of left ventricular pressure overload include hypertension, arteriosclerosis and aortic stenosis [4].

LVH is an adaptive process which occurs in response to a long-term pressure/volume overload. The mechanisms linking volume and pressure overload to LVH have been described by Grossman [5] (Figure 2). Pressure overload increases systolic pressure, which in turn increases systolic stress. This mechanical stimulus is translated through a cascade of biochemical events to a parallel addition of new myofibrils and wall thickening, which initially normalizes this systolic stress. However, the final result—a primary increase in wall thickness with no changes in internal dimension—is concentric hypertrophy. In volume overload, the primary effect is an increase in diastolic pressure, which in turn increases diastolic stress. This mechanical stimulation leads to the addition of new sarcomeres in series, increasing left ventricular dimension and so resulting in chamber enlargement. While this normalizes diastolic stress, the

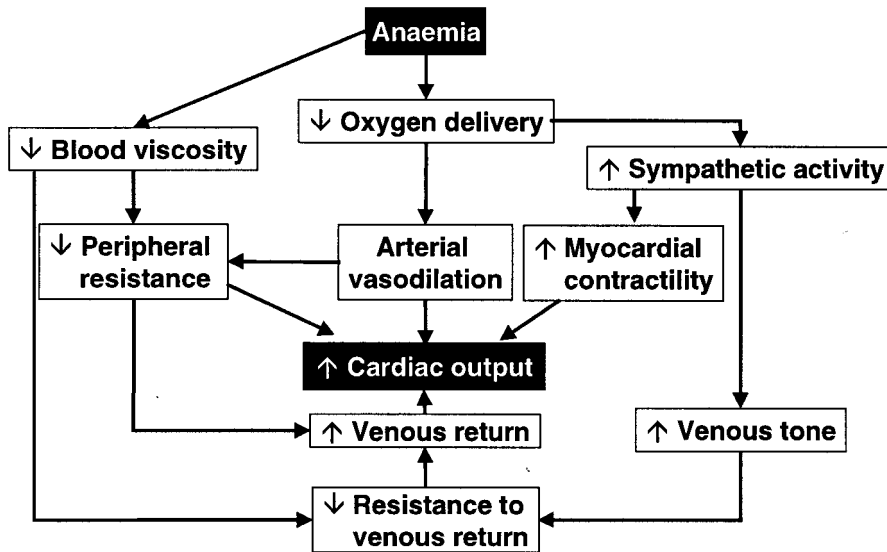


Fig. 1. Haemodynamic changes induced by anaemia (reproduced from London and Parfrey [2] with permission).

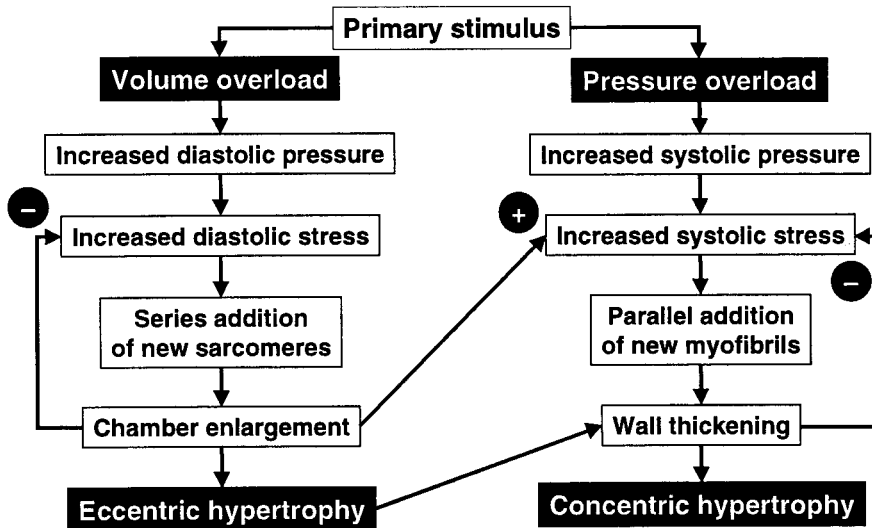


Fig. 2. Hypothesis relating wall stress and patterns of hypertrophy (adapted from Grossman [5] with permission).

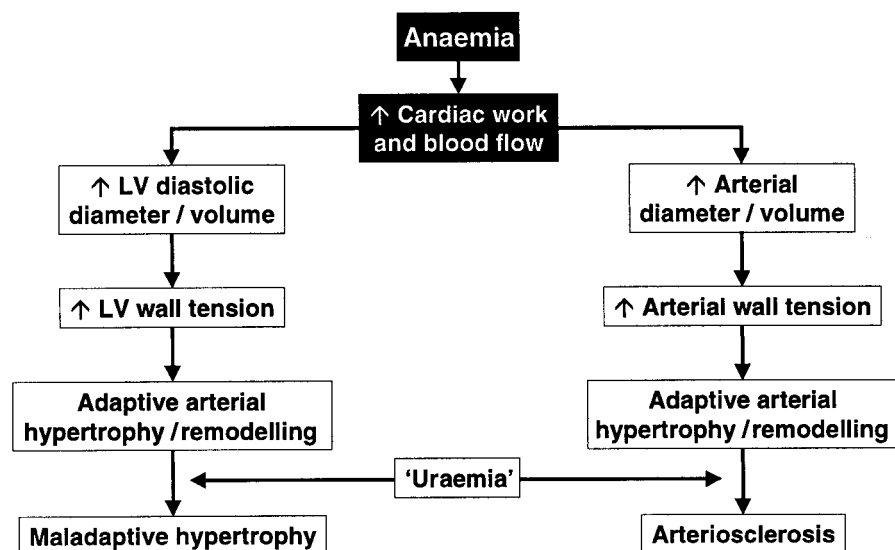


Fig. 3. Effect of anaemia on cardiovascular remodelling (adapted from Metivier *et al.* [3] with permission).

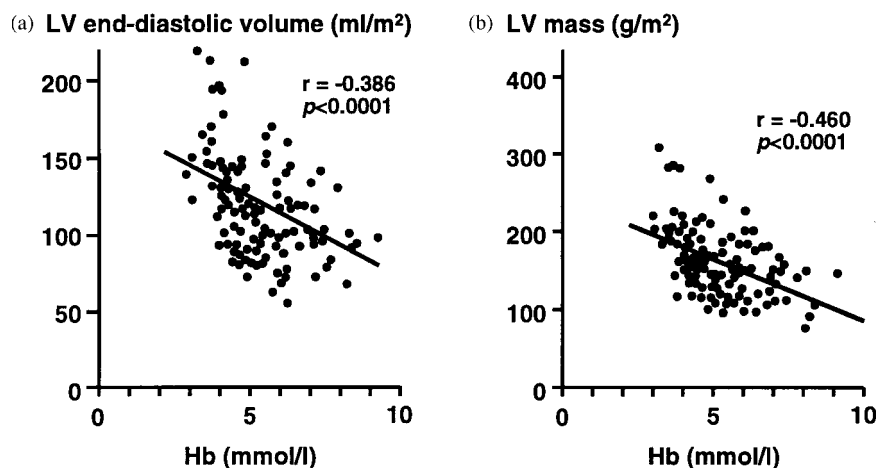


Fig. 4. Correlation between haemoglobin level and (a) left ventricular end-diastolic volume and (b) left ventricular mass (reproduced from London *et al.* [9] with permission).

chamber enlargement also increases systolic tensile stress; a secondary effect of this is parallel addition of new myofibrils and wall thickening. The final result of volume overload is eccentric hypertrophy with increased internal dimension and a parallel reciprocal increase in wall thickness, but a normal wall thickness to internal diameter ratio [5].

### Pressure and volume overload—effects on vascular remodelling

In addition to left ventricular remodelling, vascular remodelling also occurs in the arterial system. Pressure overload primarily increases wall thickness without affecting internal dimension, resulting in an increased wall mass to lumen volume ratio [6]. Volume overload primarily increases the internal lumen dimension of the arterial system with a secondary change in wall

thickness such that the wall to lumen ratio remains unaffected.

### Effects of anaemia on cardiovascular remodelling in renal patients

Under normal conditions, anaemia leads to increased cardiac work and blood flow. The effect of this on the left ventricle is to increase left ventricular diastolic diameter/volume and, subsequently, to increase left ventricular wall tension, which leads to adaptive LVH/remodelling. Similarly, on the arterial side, there is increased arterial diameter/volume followed by increased arterial wall tension, leading to adaptive arterial hypertrophy/remodelling [3]. Under normal conditions these changes are usually largely reversible. However, under uraemic conditions these changes become maladaptive, resulting in maladaptive hypertrophy and arteriosclerosis (Figure 3). Maladaptive

hypertrophy is characterized by a high degree of fibrosis, calcium deposits, and the principal functional effect, a reduction in ventricular diastolic function leading to increased left ventricular stiffness. Other consequences include haemodynamic instability and arrhythmia. Arteriosclerosis is also characterized by fibrosis and calcifications; however, the most important consequence is arterial stiffening [7], which, in ESRD patients, is responsible for an abnormal increase in systolic blood pressure [8] and is a predisposing factor for the development of atherosclerosis.

In ESRD patients there is a correlation between left ventricular end-diastolic volume and left ventricular mass with the degree of anaemia [9]. Increases in left ventricular end-diastolic volume and left ventricular mass are related to decreases in Hb levels [9] (Figure 4). Therefore, LVH progresses in parallel with changes in Hb level. Importantly, LVH has been shown to be associated with decreased survival in ESRD patients receiving renal replacement therapy. Indeed, in a study of 91 ESRD patients receiving renal replacement therapy, the relative risk associated with LVH (based on comparison of upper and lower quintiles of left ventricular mass index) was 3.7 both for all-cause mortality and for cardiac mortality [10].

## Conclusion

In conclusion, the increased risk of cardiovascular disease in renal patients is well established and

anaemia is a contributory factor to LVH in renal disease. Furthermore, cardiovascular damage starts at an early stage of renal disease and therefore early intervention to treat anaemia in these patients can prevent or delay this damage.

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