A heart price to pay for anaemia

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Introduction

Optimal tissue oxygenation requires the functional integrity of heart, lungs, and blood. If one of the partners fails in this joint task, the others have to carry some extra load. In the case of renal anaemia, the heart is requested to entertain a hyperdynamic circulation in order to compensate for the reduced oxygen transport capacity of the blood. Specifically, low blood viscosity, hypoxic vasodilatation, sympathetic activation, a-v fistula, and tachycardia force the heart to increase the cardiac output substantially in most of these patients [1,2].

Anaemia and left ventricular geometry

Obviously there is a price to pay for such profound and chronic alterations of cardiac workload, perfusion, and metabolism. In fact, left ventricular hypertrophy (LVH) is found in up to three of four patients starting on dialysis [3,4]. If we take a closer look at the hearts of such patients (but still remain at the macroscopic level), either a concentric or an eccentric form of LVH can be distinguished [4]. Such patterns are best explained as a response of the heart to either pressure overload (e.g. hypertension, resulting in concentric LVH) or volume overload (e.g. anaemia, resulting in eccentric LVH) (Figure 1) [5]. It is of interest, therefore, that analyses considering both arterial hypertension and anaemia as contributing factors suggest that pathophysiologically the latter is by no means less important. In fact, in patients starting on dialysis eccentric LVH is found twice as frequently as the concentric pattern [4]. Such findings may be of prognostic relevance, since both concentric and eccentric left ventricular hypertrophy have been identified as predictors of subsequent cardiac events [3,6,7,8].

While eccentric LVH caused by volume overload and anaemia is undisputedly a prominent risk factor and treatment target in patients with end-stage renal disease, uncertainty remains as to whether haematocrit levels should be normalized. As a cardiologist who is frequently asked about the optimal haematocrit for the heart, I must admit that I am not aware of a conclusive answer to this question. Indeed, the answer may differ for patients with coronary artery disease, congestive heart failure and/or diastolic dysfunction. Unfortunately we cannot rely too much on evidence obtained from patients without renal disease. In fact, aside from renal patients and others with some extreme forms of anaemia, the implications of chronic anaemia for adaptive changes in the cardiac geometry and perfusion have received little scientific attention.

Recently we studied the relationship between haematocrit and left ventricular geometry in a sample of the general population [9]. Structural adaptations of the heart were identified at both ends of the haematocrit spectrum, i.e. anaemia and polycythaemia. While anaemia was predominantly characterized by LV dilatation, polycythaemia was associated with a substantial increase in LV wall thickness [9] (Figure 2). The data re-emphasize, on one hand, the associations of anaemia, volume overload, and LV dilatation. Interestingly, at very low haematocrit levels we also observed an increase in LV wall thickness. This finding may reflect the pathophysiological concept that a dilatation of the left ventricle increases wall stress and, hence, causes a subsequent increase in wall thickness [5]. At the other end of the spectrum, i.e. at high haematocrit levels, LV wall thickness was also found to be increased. This finding may reflect the positive relationship of high viscosity, pressure overload, and concentric LVH [10]. Indeed, haematocrit and blood pressure levels are known to be positively associated [11].

Erythropoietin and left ventricular geometry

The data on the predominantly healthy subjects of our study sample document that the relationship between LV wall thickness and dimensions is optimal at normal to mildly decreased haematocrit levels, i.e. in the range of 35–40% in women and 38–43% in men [9]. Thus it appears that for most if not all individuals, LV geometry is best when the blood count is maintained within the normal range. At the same time, the strong, positive association between haematocrit above normal levels and LV wall thickness highlights a potential...
Fig. 1. Patterns of left ventricular geometry. An increase of left ventricular mass beyond the gender-specific cut-off points is called, by definition, left ventricular hypertrophy (LVH) (right panel). An increase in the relation of LV wall thickness/dimension (posterior + septum/ left ventricular end-diastolic dimension) beyond the cut-off point of 0.45 is called, by definition, concentric remodelling or concentric LVH (upper panel). An increase in LV mass despite a normal or even decreased relation of LV wall thickness/dimension is called eccentric LVH. The arrows indicate the most frequent pathophysiological mechanisms.

Fig. 2. Schematic relation of LV mass and haematocrit in the overall population [9]. The U-shaped curve indicates an increase of cardiac mass with both anaemia and polycythaemia, albeit the mechanisms are different (upper panel).

problem that may occur with the rapid correction of anaemia. It needs hardly a reminder at this point that one of the few side-effects of erythropoietin treatment is hypertension [12]. Moreover, erythropoietin may stimulate the renin–angiotensin or endothelin systems [13,14]. Accordingly, the afterload of the left ventricle may increase substantially with the administration of erythropoietin and increasing haematocrit levels, a potential limitation that may be of relevance particularly in patients with endothelial dysfunction (who fail to vasodilate appropriately).

In the context of concomitant cardiac disease, the situation may be even more complex. Several investigators demonstrated conclusively that erythropoietin treatment allows a regression of LVH, most notably due to a decrease in LV dimensions [15,16]. The reversibility of LV dilatation with erythropoietin treatment underscores the functional relationship of anaemia, volume overload, and eccentric left ventricular hypertrophy. Thus, theoretically, the treatment of renal anaemia with recombinant erythropoietin in patients with cardiac conditions is on solid grounds. However, some haemodynamic issues need careful attention. After all, the correction of anaemia is accompanied by increasing viscosity and peripheral resistance and, hence, an increase cardiac afterload in most patients. This is just the opposite of what we usually achieve with medical treatment for heart failure. Not surprisingly, a rapid elevation of the haematocrit into the normal range was not found to be beneficial in patients with heart failure or coronary...
artery disease [17,18]. Hence, during correction of the erythrocyte count in heart failure patients, cardiac workload has to be optimized repeatedly. Particularly, when haemoglobin levels exceed 10 g/dl, a slow correction is certainly more appealing than a rapid one [12,17].

**Diagnostic issues**

Given the specific situation of a heart-failure patient with renal anaemia, cardiac function should be evaluated carefully prior to and during the treatment with erythropoietin. In conjunction to clinical assessments, echocardiography is the most valuable diagnostic tool, as it provides information on cardiac geometry, i.e. eccentric or concentric LVH, as well as diastolic and systolic function. In anaemic patients, however, the specific pathophysiological context requires some consideration prior to interpretation of the echocardiographic findings. Specifically, the hyperdynamic circulation and compensatory increments of the circulating volume alter the loading conditions of the ventricle substantially [19], a situation that is further aggravated in case of an excessive shunt volume via the a-v fistula. As a consequence, cardiac preload increases and afterload is reduced in patients with renal anaemia with implications for the assessment of both diastolic and systolic function.

**Assessment of diastolic function**

Diastolic dysfunction secondary to hypertrophy and fibrosis of the left ventricle is a frequent finding in dialysis patients. A precise evaluation requires an invasive measurement of pressure and volume changes during the filling of the left ventricle. Nowadays, echocardiography is often preferred, since this method provides good estimates of diastolic function by assessment of the inflow pattern across the mitral valve [20]. In patients with anaemia, however, the increase in cardiac preload alters the pattern of Doppler signals that is used for the evaluation of diastolic function. In particular, the early filling (E-wave) of the left ventricle is markedly enhanced by the higher pressure in the left atrium. For the same reasons, the isovolumetric relaxation time, i.e. the time between closure of the aortic valve and opening of the mitral valve, is shortened in a patient with anaemia [21]. Both alterations (higher E-wave and shorter isovolumetric relaxation time) are just the opposite of what is seen in patients with diastolic dysfunction at normal haematocrit levels. Thus, ‘normal’ Doppler findings do not guarantee that diastolic compliance of the left ventricle is normal and a pathological Doppler profile in an anaemic patient may underestimate the extent of diastolic dysfunction.

**Assessment of systolic function**

The reduction of cardiac afterload, secondary to low viscosity and reduced peripheral resistance, facilitates systolic cardiac ejection in patients with renal anaemia [19,22]. Thus ejection fraction or fractional shortening of the left ventricle may appear relatively normal even when the systolic function is impaired. A more precise measure may be the assessment of mid-wall fibre shortening [23]. However, this parameter is not frequently used for routine evaluation.

Taken together, in patients with anaemia the interpretation of the echocardiography findings should be rather cautious. Accordingly, repeated clinical evaluations, inquires about clinical performance, and exercise tolerability should accompany the treatment of an anaemic patient. Moreover, in a cardiac patient the correction of anaemia should be slow and careful above a haemoglobin level of 10 g/dl. In addition, in the presence of heart failure, erythropoietin treatment should be facilitated by sufficient afterload reduction (ACE inhibitors) and by avoidance of excessive volume fluctuations. If these caveats are respected, strong evidence suggests that even patients with severe heart failure will benefit substantially from the treatment of anaemia [24]. Finally, given the foreseeable consequences of low haematocrit levels, early treatment may help to avoid the consecutive development of LV dilatation and eccentric LVH. Thus, prevention of renal anaemia may be more efficient than its treatment that comes, after all, too late to pay a mortgage taken from the heart.

**Acknowledgements**

Supported by a grant of the Deutsche Forschungsgemeinschaft (German Research Society) (DFG Schu 672/9-1, Schu 672/10-1, and Schu 672/12-1) and the Bundesministerium für Forschung und Technologie (Federal Ministry of Research and Technology) (HWH, HS, AD), the Vaillant Stiftung (Vaillant Foundation), Munich, the Deutsche Stiftung für Herzforschung (German Foundation of Heart Research), Frankfurt, the Ernst and Berta Grimmke Stiftung (Ernst and Berta Grimmke Foundation) (HS), and a research grant from the R. W. Johnson Pharmaceutical Research, Raritan, NJ (HWH, HS).

**References**


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