

## SCIENTIFIC LETTER

## Anaemia in chronic heart failure: what is its frequency in the UK and its underlying causes?

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In two recent studies from Israel, Silverberg and colleagues noted that anaemia was common in chronic heart failure (CHF).<sup>1,2</sup> Moreover, treatment with combined erythropoietin and intravenous ferrous sulfate not only increased haemoglobin concentrations but, more importantly, was associated with improvements in cardiac function, New York Heart Association (NYHA) functional class, renal function, and falls in the need for diuretics and hospitalisation. The importance of anaemia in CHF was recently highlighted by data from the SOLVD study where anaemia was found to be a risk factor for mortality.<sup>3</sup> Two questions now arise. Firstly, how common is anaemia in CHF patients in the UK? Secondly, what causes this anaemia in CHF? This second question is pertinent because there are numerous possible causes of anaemia in such patients. For example, aspirin use is widespread in CHF patients, raising the possibility of iron deficiency anaemia. Renal dysfunction is also common, raising the possibility of an anaemia of chronic disorder. Since CHF patients are elderly, coincidental hypothyroidism or pernicious anaemia could also contribute to the anaemia. We therefore set out to assess these two questions retrospectively. After all, erythropoietin would not be an appropriate treatment in CHF anaemia where iron deficiency or pernicious anaemia were identified as the cause of the anaemia.

## METHODS

We decided to survey cases of NYHA functional class IV CHF because Silverberg and colleagues suggested that anaemia was particularly common in this group.<sup>1,2</sup> A total of 269 CHF patients requiring acute admission to Ninewells Hospital, Dundee were selected at random retrospectively between June 1998 and December 2000. Those with CHF were targeted from discharge letters and from selection from admission files to the acute receiving ward in Ninewells Hospital. A haemoglobin concentration of 11 g/dl or less was selected as our cut-off for anaemia. This was a compromise figure because the reference range for haemoglobin usually has 12.5–13.5 g/dl as its lower limit, whereas clinical trials of anaemia treatment in haematology patients often use the cutoff of 10–11 g/dl as entry criteria. Our overall feeling was that clinicians would be unlikely to embark on erythropoietin treatment when the haemoglobin concentration was 11.5 g/dl, whereas they might institute such treatment in a symptomatic CHF patient with a haemoglobin concentration of 10.5 g/dl. This group was further subdivided into microcytic, normocytic, and macrocytic anaemia with a mean cell volume (MCV) < 76 fl, 76–96 fl, and > 96 fl, respectively. In each of these groups it was noted if any patients had renal impairment (creatinine on admission  $\geq 160 \mu\text{mol/l}$ ), whether ferritin was low for age or sex (see table 1 for reference values used at Ninewells Hospital), whether the B12 or folate concentrations were low (< 200 ng/l and < 2.1  $\mu\text{g/l}$ , respectively), and if possible hypothyroidism was present (thyroid stimulating hormone (TSH) > 4 mu/l).

**Table 1** Ninewells Hospital biochemical laboratories reference values for ferritin relative to age and sex

Sex	Age (years)	Ferritin ( $\mu\text{g/l}$ )
Female	18–45	21–70
Male	18–45	53–220
Female	45–55	34–110
Male	45–55	75–350
Female	55–60	41–120
Male	55–60	75–400
Female and male	>60	15–300

**Table 2** Potential causes of anaemia in chronic heart failure patients

	Mean cell volume			Total
	<76 fl	76–96 fl	>96 fl	
Number patients	3	28	8	39
Creatinine $\geq 160 \mu\text{mol/l}$	1/3	12/28	4/8	17/39
Ferritin low*	1/3	0/9	0/4	1/16
B12 /folate low	0/2	0/10	0/5	0/17
TSH $\geq 4 \text{ mu/l}$ *	0/3	6/15	1/3	7/21

\*Ninewells Hospital laboratory reference ranges (see table 1 for ferritin ranges).

TSH, thyroid stimulating hormone.

## RESULTS

Thirty nine of the 269 patients (14.4%) selected had a mean haemoglobin concentration of  $\leq 11 \text{ g/dl}$ . Of these 39 patients, three were microcytic and eight were macrocytic. It is difficult to compare this figure with Silverberg's work since his cutoff was unrealistically high (haemoglobin concentration < 12 g/dl) which may be why 79% of his NYHA class IV patients were quoted as being anaemic.

Of the group classified as having a microcytic anaemia (MCV < 76 fl) ferritin was low in only one of three patients (table 2<sup>2</sup>). However, this group is too small for any detailed analysis of the precise cause of the anaemia.

In the patients with a normocytic anaemia (MCV 76–96 fl), 43% of them had evidence of renal impairment (creatinine  $\geq 160 \mu\text{mol/l}$ ) and 40% had evidence of possible hypothyroidism (TSH > 4 mu/l), but no patient had evidence of any deficiency of any haematinic (iron, B12, folate) (table 2).

Eight patients (21%) were found to have a macrocytic anaemia, half of whom had evidence of renal impairment with

**Abbreviations:** CHF, chronic heart failure; MCV, mean cell volume; NYHA, New York Heart Association; SOLVD, studies of left ventricular dysfunction; TSH, thyroid stimulating hormone

one isolated case of possible hypothyroidism. Interestingly, as in the normocytic group, no patient had evidence of any haematinic deficiency (iron, B12, folate).

Looking at the group as a whole, renal impairment was present in 44% and possible hypothyroidism was present in one third of those who were assessed for hypothyroidism. However, despite 40% of them having either a microcytic or macrocytic anaemia, a specific haematinic deficiency (iron, B12, folate) was virtually absent.

## DISCUSSION

We found that anaemia in CHF is common, occurring in 14.4% of our hospitalised population. The studies by Silverberg and colleagues suggest that anaemia can aggravate the symptoms of heart failure, and that either active or prophylactic treatment of anaemia will improve symptoms and signs and decrease the need for hospitalisation.<sup>1,2</sup> Therefore, a case can now be made for treating anaemia in CHF whenever it is found. This begs the question: what is the correct way of treating anaemia in each case of CHF?

Before this study, we had anticipated that the cause of the anaemia in CHF would be heterogeneous and that erythropoietin would only be appropriate for a minority who turned out to have a true anaemia of chronic disorder, whether it be caused by renal impairment or not. However, what is striking from our results is that a haematinic deficiency of any kind was exceedingly rare. Possible hypothyroidism was found in a small group, but it is difficult to know whether this was the cause of the anaemia or not in any case. Most of the anaemia

seen in CHF does appear to be an anaemia of chronic disorder, some of which could be caused by renal dysfunction and some by an unknown cause. In either case, the erythropoietin regimen as proposed by Silverberg and colleagues<sup>1,2</sup> might be the only therapeutic option available in the majority of anaemic CHF patients. Further work is therefore required to confirm or refute the benefits of erythropoietin treatment reported by Silverberg and colleagues.<sup>1,2</sup>

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