



## LETTER TO THE EDITOR

### Anemia and iron in heart failure – A brief comment



### Anemia e ferro na insuficiência cardíaca – um breve comentário

I read with interest a letter mentioning our paper on “Anti-troponin I antibodies in renal transplant patients”, recently published.<sup>1</sup> Since the text is on a different topic, iron metabolism in heart failure, I will start by briefly commenting on this latter theme.

Medical textbooks have traditionally paid a considerable degree of attention to anemia and to iron deficiency. The underlying line of reasoning is that as iron is an essential element for the production of erythrocytes, insufficient body iron stores may lead to anemia, a situation that can be corrected by the administration of iron. Conventional medical wisdom has been that it is better to have a hemoglobin concentration in the normal range, rather than a lower one.

Data obtained in chronic renal failure patients with the use of erythropoiesis-stimulating agents (compared to placebo) caused a shift in medical thinking on the subject under consideration. Studies by Singh et al.,<sup>2</sup> Drueke et al.<sup>3</sup> and Pfeffer et al.<sup>4</sup> have clearly shown that normal or near-normal values for hemoglobin lead to worse outcomes in patients with chronic renal failure, compared to lower values, leading to the current policy of avoiding hemoglobin values greater than 11.5 g/dl in these patients (therefore, normal is not always better).

It was not until the turn of the millennium that an important regulator of iron metabolism<sup>5</sup> was discovered – hepcidin.<sup>6,7</sup> As iron is important not only for human cells but also for invading microbial cells, the human body has a hepcidin-based mechanism to withdraw iron from the circulation in the presence of infection.<sup>5</sup> Many inflammatory states would appear to be interpreted as stimuli for the action of hepcidin – giving rise to the so-called anemia of chronic disease. In a study carried out in preschool children in Africa (in a region with a high incidence of malaria), Sazawal et al. showed that routine prophylactic supplementation with iron and folic acid resulted in an increased risk of severe illness and death.<sup>8</sup>

With regard to heart failure, a condition frequently associated with anemia (and also with inflammation<sup>9</sup>), Swedberg et al. showed that darbepoetin alfa did not improve clinical outcomes in this setting.<sup>10</sup> Adverse thromboembolic events were in fact increased in the intervention patient group.<sup>10</sup> Anemia in heart failure may have different types of causes, one of which is the action of angiotensin-converting enzyme inhibitors.<sup>11</sup> Enalapril has been shown to increase the incidence of anemia in patients with heart failure.<sup>11</sup> Heparin was shown to be decreased in patients with heart failure and anemia,<sup>12</sup> and has an uncertain role in this disease (unlike the case of hemodialysis patients, who have increased hepcidin levels<sup>13</sup>).

Anemia is associated with increased mortality in patients with heart failure, however it is unclear whether it is a marker or a mediator of increased mortality risk in this setting.<sup>14</sup> Ferric carboxymaltose has been used in patients with heart failure and “iron deficiency”, with improvement in symptoms, functional capacity, and quality of life.<sup>15,16</sup> However, data are available for only up to one year of therapy, and the longer-term effects of ferric carboxymaltose are unclear. Iron deficiency was diagnosed if ferritin <100 ng/ml or 100–299/300 ng/ml if transferrin saturation <20%, meaning that it is uncertain whether total body iron stores were decreased in all patients studied.<sup>15,16</sup> “Iron deficiency”, under the same criteria, has been shown to act as a marker for an unfavorable prognosis in patients with heart failure.<sup>17,18</sup>

Getting back to the comment on our text,<sup>1</sup> we did not report that “the levels of antibodies were associated with reduced left ventricular ejection fraction”, neither did we state that “inflammatory mediators such as antibodies can be used as a marker of cardiac dysfunction”.

Moreover, I would certainly not agree with the concept that erythropoietin “seems to be an efficient therapy” for heart failure (as the data presented above<sup>10</sup> show).

However, we did publish a case report,<sup>19</sup> mentioned in our text, in which high titers of anti-troponin I antibodies were associated with the partial reversibility of a clinical picture of dilated cardiomyopathy, after immunosuppressive drugs were used. We presented the hypothesis that “the syndrome of reversible cardiomyopathy seen after renal transplantation is associated with immunosuppression therapy acting on immunological mechanisms previously at play”.<sup>19</sup>

The speculation that anti-troponin I antibodies, acting as inflammatory mediators, could “lead to the inhibition of iron absorption at the duodenal level” – and this would

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seem to be the major point to be considered in the text – is worthy of consideration, in my view.

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