

## President's Page

## Heart Failure in $\beta$ -Thalassaemia: A Local or Universal Health Problem?

DIMITRIOS T. KREMASTINOS

2nd University Department of Cardiology, Attikon University Hospital, Athens, Greece



**B**-thalassaemia belongs to the group of haemoglobinopathies, which are the most common monogenic disorders in the world population and were the first diseases to be analysed by recombinant DNA technology. Homozygous  $\beta$ -thalassaemia is characterised by severe haemolytic anaemia associated with chronic organ damage and a high incidence of infections. It extends well beyond the boundaries of the Mediterranean Sea, in a line reaching countries of the Middle and Far East. However, nowadays  $\beta$ -thalassaemia seems to have become a universal health problem, since thousands of people have emigrated from those countries to the EU and USA.

Despite progress in chelation therapy, heart failure is still the main cause of death in patients with  $\beta$ -thalassaemia major, since approximately 70-80% of  $\beta$ -thalassaemic patients die from this cause.<sup>1,2</sup> Iron deposition is considered the fundamental aetiological factor of organ dysfunction and failure in this disease. However, immunogenetic abnormalities and myopericarditis undoubtedly contribute to the pathogenesis of heart failure.

The severity of iron toxicity in  $\beta$ -thalassaemia major seems to be related to the magnitude of the body's iron burden. The exact mechanism of iron overload toxicity has been uncertain for many years. Via the iron-driven Fenton and Haber-Weiss reactions, the non-transferrin plasma iron, in its bivalent or trivalent form, has a high toxicity through the formation of hydroxyl radicals (OH). This leads to peroxidative damage of membrane lipids and proteins. Imbalance between the production of free oxygen radicals and antioxidant defence mechanisms can result in oxidative stress and human disease. In the heart, the imbalance between free radicals and antioxidant mechanisms is

manifested as impaired function of the mitochondrial inner-membrane respiratory chain, resulting in abnormal energy metabolism expressed clinically in the form of fatal cardiomyopathy. Apart from iron overload, it has been demonstrated recently by our group that myocarditis appears to be involved in the pathogenesis of left ventricular failure in approximately 4% of patients with heart failure. As shown in animal models, oxygen free radicals may also contribute to the pathogenesis of infectious myocarditis.<sup>3-7</sup>

The clinical presentation of heart failure is mainly expressed as left ventricular systolic or diastolic dysfunction. Diastolic dysfunction appears early in the patient's life, progresses slowly, and leads to left ventricular restrictive abnormalities, pulmonary hypertension, right ventricular dilatation and failure.<sup>8</sup> Systolic dysfunction presents as the dilated type of cardiomyopathy, leading to death within one year after the onset of heart failure symptoms.<sup>9</sup> However, by increasing the total number of blood transfusions and intensification of iron chelation therapy we reported a five-year survival of 48%, approximately similar to the survival observed in the general population with heart failure.<sup>9</sup>

Myocardial iron deposition does not affect left ventricular relaxation but directly causes left ventricular myocardial diastolic dysfunction, which is expressed as an echo-Doppler restrictive pattern.<sup>10</sup> Meanwhile, it was also reported recently that echo-Doppler indices do not detect mild diastolic dysfunction, which is characterised by increased filling pressures on exertion.<sup>11,12</sup> In this respect we have found that an increased level of the NT-pro-BNP biomarker expresses left ventricular early diastolic dysfunction before

the conventional echo-Doppler indices become apparently abnormal in patients with  $\beta$ -thalassaemia major.<sup>13</sup> Therefore, this biomarker may be used in clinical practice, since a progressive increase in NT-pro-BNP for an individual patient could be a signal for intensification of chelation therapy and improvement in haemoglobin levels before the heart failure symptoms become apparent. This strategy is expected to further improve the life expectancy of the  $\beta$ -thalassaemic population.

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