Brief Communication

Acta Hæmatologica

Acta Haematol 2007;118:167–168
DOI: 10.1159/000108767

Received: June 7, 2007
Accepted after revision: July 18, 2007
Published online: September 21, 2007

Partial Reversal of Hemolysis-Associated Pulmonary Arterial Hypertension in Response to Oral Administration of L-Arginine in a Patient with Hereditary Spherocytosis

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Hemolysis-associated pulmonary hypertension has been reported in a variety of hemolytic disorders and is considered to be caused, amongst others such as nitric oxide scavenging by cell free plasma hemoglobin, by deficiency of L-arginine, the precursor of nitric oxide [1]. Current management consists of treatment with sildenafil and bosentan. Hereditary spherocytosis consists of a group of hemolytic anemias caused by defects in the proteins involved in the vertical interactions between the membrane skeleton and the lipid bilayer of the red cell. We report the first case of partial reversal of hemolysis-associated pulmonary arterial hypertension in response to oral administration of L-arginine in a patient with hereditary spherocytosis.

A 47-year-old Caucasian man presented with complaints of recurrent chest pains, gradually progressive dyspnea, current New York Heart Association class 2, and fatigue. He had undergone splenectomy at the age of 15 years and cholecystectomy at the age of 22 years. Apart from a prominent, fixed split second heart sound, physical examination was normal. The resting 12-lead electrocardiogram showed signs of right ventricular pressure overload. Laboratory tests, including full blood count, liver functions, cardiac enzymes, arterial blood gas and antinuclear factor, were all normal, apart from mildly elevated D-dimers (0.61 mg/l, normal <0.5 mg/l) and decreased haptoglobin (0.08 g/l). Doppler echocardiography showed mild right ventricular dilation, hypertrophy, impaired right ventricular myocardial performance index (0.63, normal 0.28 ± 0.04) and elevated right ventricular peak systolic pressures of approximately 45 mm Hg (modified Bernoulli equation), without evidence of an intracardiac shunt. Contrast-enhanced 64-slice computed tomography excluded the presence of thrombi in the right heart, the proximal and the peripheral pulmonary arteries, and showed normal pulmonary venous drainage. Underlying structural pulmonary disease and coronary artery disease were excluded. Invasive right-sided hemodynamic evaluation confirmed pulmonary arterial hypertension (mean pressures of 40 mm Hg), with normal oxygen saturations in the vena cava, atrium, ventricle and pulmonary artery (table 1). Delayed contrast-enhanced cardiac magnetic resonance did not reveal focal septal or right ventricular fibrosis. We started warfarin (international normalized ratio 2–4), aspirin 100 mg daily and L-arginine orally at a dose of 100 mg/kg 3 times daily. Reassessment after 4 weeks of treatment with L-arginine showed normalization of electrocardiographic right ventricular repolarization abnormalities, a decrease in right-sided pressures (mean arterial pressures of 34 mm Hg) and pulmonary vascular resistance (649–479 dyne·s/cm^5/m^2) (table 1).

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Table 1. Hemodynamic measurements

	mean SBP mm Hg	mean RAP mm Hg	mean RVEDP mm Hg	mean PAP mm Hg	mean PCWP mm Hg	mean CI l/min	SVRI, dyne·s/cm^5/m^2	PVRI, dyne·s/cm^5/m^2	RVSWI g·m/m^2
Baseline	95	12	13	40	13	3.33	1,993	649	17.6
90 min after a single oral dose of 100 mg/kg L-arginine	95	12	13	40	12	3.25	2,043	689	17.2
After 200 μg intravenous nitroglycerine	84	9	9	34	12	3.39	1,796	519	16.0
After 1 month of TDS oral 100 mg/kg L-arginine	93	7	2	34	14	3.34	2,060	479	17.0
After 200 μg intravenous nitroglycerine	80	5	1	32	13	2.96	2,027	514	15.1

SBP = Systolic blood pressure; RAP = right atrial pressure; RVEDP = right ventricular end-diastolic pressure; PAP = pulmonary arterial pressure; PCWP = pulmonary capillary weight pressure; CI = cardiac index; SVRI = systemic vascular resistance index; PVRI = pulmonary vascular resistance index; RVSWI = right ventricular stroke work index; TDS = 3 times daily.

L-Arginine is the nitrogen donor for synthesis of nitric oxide, a potent vasodilator. Low plasma L-arginine levels have been discovered in patients with pulmonary hypertension, and supplementation has improved pulmonary artery pressures and hemodynamics in patients with primary and secondary pulmonary hypertension [2–5]. In hemolytic conditions, such as congenital spherocytosis, release of free hemoglobin, red cell arginase and superoxide results in a reduction of the nitric oxide synthase substrate, L-arginine and reduced production of nitric oxide, causing endothelial dysfunction and pulmonary arterial hypertension [1, 6]. Free hemoglobin itself also functions as a very potent nitric oxide scavenger [7]. Reduced bioavailability of nitric oxide amplifies cell signaling pathways involving endothelial cell adhesion molecules, which orchestrate the recruitment and binding of inflammatory cells to vascular endothelium [1]. Our findings suggest that in addition to treatment with sildenafil or bosentan, supplementation with L-arginine may be of value in patients with this condition.

Considering the significant morbidity and poor prognosis of pulmonary arterial hypertension, early detection and adequate treatment may alter the outcome [8]. Further studies are planned to confirm our results in a larger cohort of patients.

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