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L-Arginine therapy in Raynaud's phenomenon?

Angelo Agostoni [1], Bianca Marasini [1], Maria Luisa Biondi [1], Cristina Bassani [1], Anna Cazzaniga [1], Bianca Bottasso [2], and Massimo Cugno [1]

[1] Department of Clinical Medicine, University of Milan, "S. Paolo" Hospital, Via di Rudini 8, I-20142 Milan, Italy
[2] A. Bianchi Bonomi Hemophilia and Thrombosis Centre, University of Milan, Milan, Italy

Summary. Since L-Arginine is the substrate for nitric oxide synthesis by vascular endothelial cells the effects of L-arginine treatment on the digital vascular response to local stimuli were investigated in patients with primary or secondary Raynaud's phenomenon. After therapy, patients with Raynaud's phenomenon secondary to systemic sclerosis showed: (1) higher digital vasodilation after local warming, (2) cold-induced digital vasodilation, and (3) increase of plasma levels of tissue-type plasminogen activator.

Key words: L-Arginine – Raynaud's phenomenon – Strain-gauge plethysmography – Systemic sclerosis – Tissue-type plasminogen activator

Introduction

Some experimental evidence has suggested that an impairment of nitric oxide production in damaged or L-arginine-depleted endothelial cells might be responsible for abnormalities in vascular reactivity [1, 3, 5]. The proposed role for L-arginine, the substrate for nitric oxide synthesis by vascular endothelial cells, in peripheral vasodilation [4, 7, 9] prompted us to study the effect of L-arginine treatment on the digital vascular response to local stimuli in patients with Raynaud's phenomenon.

Patients and methods

L-Arginine monochloride (Damor Farmaceutici, Naples, Italy) was given orally, 4 g twice daily, to 12 patients with Raynaud's phenomenon (5 with primary Raynaud's phenomenon and 7 with systemic sclerosis-associated Raynaud's phenomenon) aged 18–62 years, with no evidence of arterial hypertension or renal failure. All patients gave their informed consent. No vasoactive drug was given throughout the study. Digital pulse amplitude was measured by strain-gauge plethysmography under baseline conditions after 30 min acclimatization, and again with the test hand immersed in water at 42 °C (10 min) and then at 16 °C (2 min). Plasma levels of tissue-type plasminogen activator (t-PA) were determined by an enzyme-linked immunosorbent assay method (American Diagnostica, New York, USA). All measurements were performed before and 1 month after therapy. Statistical analysis was performed using the Wilcoxon-Mann-Whitney non-parametric test for paired and unpaired data.

Offprint requests to: A. Agostoni

Results

Pre-treatment warming of the test hand resulted in vasodilation in all patients. Warming after L-arginine treatment produced a further increase in digital pulse amplitude, significant only in patients with systemic sclerosis. Moreover, in these patients, but not in those with primary Raynaud's phenomenon, hand cooling resulted in digital vasodilation after L-arginine treatment (Fig. 1). Plasma levels of t-PA significantly increased after therapy in secondary patients [12.6 ± 1.3 vs 14.5 ± 1.6 ng/ml (mean $\pm$ SEM) pre- vs post-treatment, $P < 0.05$], but not in primary patients (9.0 ± 0.8 vs 8.3 ± 1.1). Heart rate and blood pressure remained unchanged.

Discussion

We have no explanation for the unexpected L-arginine-associated vasodilation of digital vessels in systemic sclerosis patients after local cooling, since cold-induced vasodilation is normally observed only after prolonged or severe cooling, and vasodilators, when beneficial, usually reduce but do not eliminate cold-induced digital vasoconstriction even in Raynaud's patients. However, it is tempting to speculate that L-arginine-associated changes in digital vascular reactivity may be related to an endothelial effect of L-arginine. Systemic sclerosis patients, but not patients with primary Raynaud's phenomenon, should have endothelial damage [8]. Indeed, L-arginine may not relax normal vascular tissue because high endothelial levels of the precursor amino acid may be present, which would prevent the formation of nitric oxide

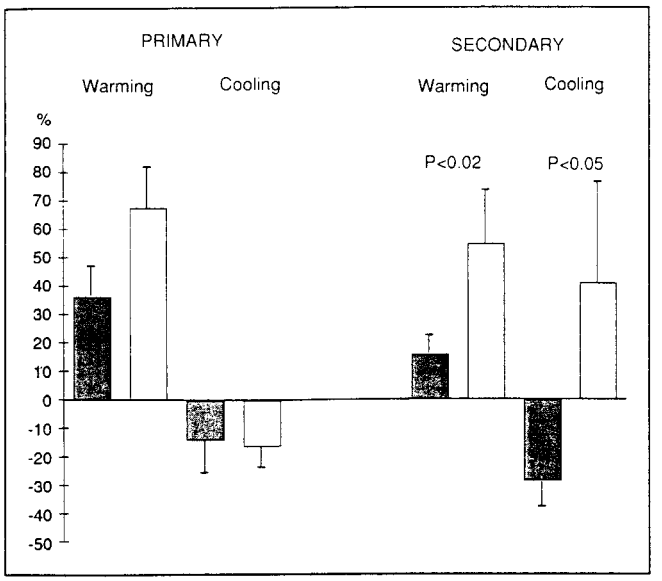

Fig. 1. Percentage changes in digital pulse amplitude (mean ± SEM). L-Arginine-associated changes in digital pulse amplitude after local warming or cooling in 5 patients with primary Raynaud's phenomenon and 7 with systemic sclerosis-associated Raynaud's phenomenon (■, pre-treatment changes; □, post-treatment changes). Secondary Raynaud's phenomenon, warming pre-treatment vs post treatment $P < 0.02$; cooling pre-treatment vs post-treatment $P < 0.05$

from L-arginine from becoming the rate-limiting step. This would become rate-limiting only under conditions of endothelial cell depletion of L-arginine or if the enzyme involved in the formation of nitric oxide from L-arginine is impaired [1, 3, 5].

Moreover, this study shows that plasma levels of t-PA, a product of endothelial cells, which are increased per se in secondary Raynaud's phenomenon [6], are further increased after L-arginine treatment. These findings might be consistent with endothelial damage and repair and indicate an endothelial effect of L-arginine. However, Fritzler and Hart [2] recently proposed recombinant t-PA treatment in patients with secondary Raynaud's phenomenon.

No attempt was made to record a subjective benefit of L-arginine treatment since the study was performed in the summer when the majority of patients were symptom free. It is important to emphasize the limitations of our results since this was only a preliminary study on a small number of patients. More studies are needed to determine whether L-arginine has a role in treating the endothelial damage of patients with secondary Raynaud's phenomenon.

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