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Oscillatory flow suppression improves inflammation in chronic venous disease

Paolo Zamboni, MD,[a,b,*] Paolo Spath, MD,[a,b] Veronica Tisato, PhD,[a] Mirko Tessari, PhD,[a,b] Patrizia Dalla Caneva, MD,[a,b] Erica Menegatti, PhD,[a,b] Savino Occhionorelli, MD,[a,b] Sergio Gianesini, MD,[a,b] and Paola Secchiero, PhD[a]

[a] Department of Morphology, Surgery and Experimental Medicine, University of Ferrara, Ferrara, Italy
[b] Vascular Disease Center, Unit of Translational Surgery, University of Ferrara, Ferrara, Italy

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ABSTRACT

Background: To assess if suppression of the oscillatory component of reflux may improve the inflammatory phenotype in chronic venous disease (CVD).

Materials and methods: From 193 CVD patients, we selected 54 (13 males, 41 females, CEAP C2-4EpAsPr) for a blinded, case-control prospective investigation. All of them underwent echo-color-Doppler assessment of reflux parameters. In the same patients a blood systemic assessment of 19 inflammatory cytokines was obtained. Follow-up lasted 6 months. The control group (C) was constituted by 21 homogenous CVD patients, unselected and not operated.

Results: Thirty-one of 54 patients were excluded from post-operative evaluation in consequence of reported new other inflammatory episodes. Twenty-three (23) completed the follow up, showing the suppression of the oscillatory component of venous reflux; 4 of the 19 cytokines decreased significantly after the procedure: Tumor Necrosis Factor-α (TNFα), Granulocyte Colony Stimulating Factor (G-CSF), Interferon gamma-induced Protein 10 (IP-10), Interleukin-15 (IL-15). Particularly, TNFα and IP-10 even returned inside a physiological range: 5.3 ± 2.7 to 4.2 ± 2.2 pg/mL ($P < 0.003$) and from 303.7 ± 168.4 to 254.0 ± 151.6 pg/mL ($P < 0.024$), respectively. Both cytokines showed a weak but significant correlation with parameters of oscillatory flow correction. Finally, three cytokines implicated in repair and remodeling of tissue, Epidermal Growth Factor, Monocyte Chemoattractant Protein-1 and Platelet Derived Growth Factor-BB (PDGF-BB), significantly increased. Our findings are further reinforced by the significant changes of the same cytokines when compared to C group.

Conclusions: The surgical suppression of the oscillatory component of reflux modulates the inflammatory phenotype, suggesting a pivotal role of flow among factors concurring to inflammation in CVD.

* *Corresponding author*. Vascular Disease Center, Unit of Translational Surgery, University of Ferrara, Via Aldo Moro 8, 44124 Cona, Ferrara, Italy. Tel.: +39 0532236524; fax: +39 0532237144.
E-mail address: paolozamboni@icloud.com (P. Zamboni).
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Introduction

Ethiopathogenesis of chronic venous disease (CVD) is almost completely obscure. The pathophysiology is dominated by lower limbs venous hypertension. In most cases, venous hypertension is caused by reflux through incompetent valves, disregarding the incompetence origin from a primary valvular failure or secondary to parietal dilation.[1-3]

It is well known how in course of CVD, the inflammatory process is dominated by the so-called white cell trapping phenomenon.[4,5] On the endothelium side, inflammation is characterized by a cytokine cascade with activation of matrix metallo proteinases and sustained remodeling of the valves and venous wall.[6-9] However, the effective contribution of hemodynamics to the inflammatory phenotype of the endothelium is unknown. *In vitro* investigations, aimed to understand the contribution of flow to atherosclerosis, have already demonstrated the direct relationship between hemodynamic forces and endothelial expression,[10] whereas a laminar flow is associated with low-inflamed vessel walls,[11] an oscillatory flow is linked to a pro-inflammatory endothelial lining.[12]

Reflux in the veins of the lower limbs is a perfect example of oscillatory flow.[1,13,14] There is an upward component at muscular systole followed by a reverse flow wave at muscular diastole (Fig. 1).

Varicose veins ablation permitted *ex vivo* assessment of inflammatory molecules released by the endothelial cells[9] in the same segments where reflux hemodynamics has been preoperatively measured. Preliminary experience in such ex-vivo setting showed an interesting correlation between reflux as an oscillatory flow and release of endothelial cytokines from varicose veins.[15] This result suggests the role of flow as an underestimated factor in modulating cytokines release also in CVD. Moreover, most of the cytokines released *ex vivo* by the venous endothelium were also found increased in the blood, becoming potential biomarkers of the CVD inflammatory process.[16]

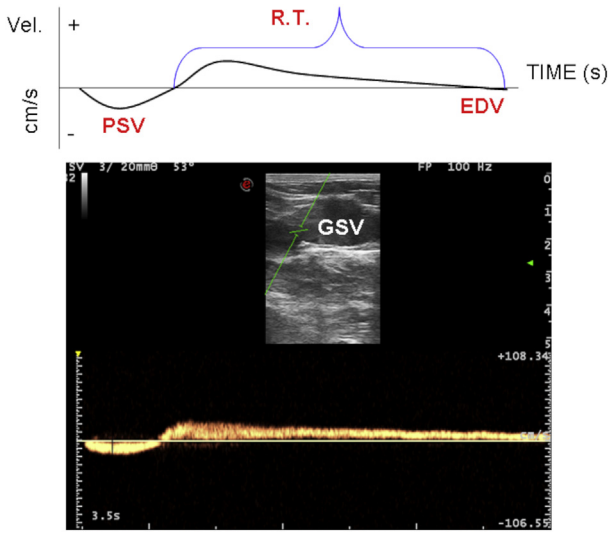

Fig. 1 – The classic oscillatory flow of venous reflux, with bi-directional positive and negative components is depicted. Top: exemplification of the parameter assessed, peak systolic velocity (PSV), end diastolic velocity (EDV), and reflux time (RT). Bottom: duplex scanning of the great saphenous vein (GSV) 15 cm below the junction, longitudinal access, where the parameters were assessed. (Color version of figure is available online.)

The aim of the present work was to verify how the surgical suppression of the oscillatory component of reflux may modulate the inflammatory phenotype assessed by measurement of circulating endothelial cytokines.

Materials and methods

Patients population and samples collection

From a cohort of 193 patients affected by primary CVD, we selected patients for the present study according to the following inclusion criteria:

- Primary CVD
- CEAP Clinical class ranging from 2 to 4
- Reflux confined to the GSV territory
- Type I shunt[17,18]
- Type III shunt with competent terminal valve[19]
- Age 18-65 y
- BMI $\leq$28
- Willing to participate to the study

Exclusion criteria were the following:

- Absence of concomitant acute and chronic inflammatory diseases
- Active and healed venous ulceration
- Smoking
- Absence of significant comorbidities affecting the cardiovascular, hepatic, renal, and nervous apparatus
- Concomitant reflux in the SSV, deep venous system, pelvic veins, and controlateral limb
- Type III shunt with incompetent GSV terminal valve[17,18]

Fifty-four patients (13 male and 41 female, mean age 52.25 $\pm$ 13.73) fulfilled the inclusion and exclusion criteria and entered the study. The study was approved by the Ferrara University—Hospital Ethical Committee.

All the patients underwent an echo-color-Doppler (ECD) investigation (Esaote My-Lab 70, Esaote Genoa, Italy) in standing position with complete scanning of the great saphenous vein (GSV) and small saphenous vein (SSV) systems, including junctions and tributaries. In addition, the main trunk of the deep venous system and the perforators were completely examined. Calf muscular pump was elicited by manual squeezing, considering as reflux the detection of a reverse flow lasting more than 0.5 s in all the examined segments. At the junction level, competence of the valve was also tested, as previously described, by means of a combination of squeezing and Valsalva maneuver, with the Doppler sample volume placed on the femoral side of the terminal GSV valve.[13,14,19]

Reflux elimination test was used to differentiate between type I and Type III shunt.[19]