Venolymphatic Diseases and Inflammation

(Anti-inflammatory effects of compression therapy: the state-of-art - *Cinderella role for Compression?)*

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Inflammation

Defense mechanism which is activated in response to traumas, tissue alterations

Sequence of biological events, which occur in response to a harmful non-specific stimulus, aimed to:

- **Dilute, Neutralize, Destroy the harmful agent**
- **Reduce the tissue damage to the minimum**
- **Prepare organism to combat the pathogenic agent**
- **Prepare the inflammed area for the repair and Initiate the repair pathways**

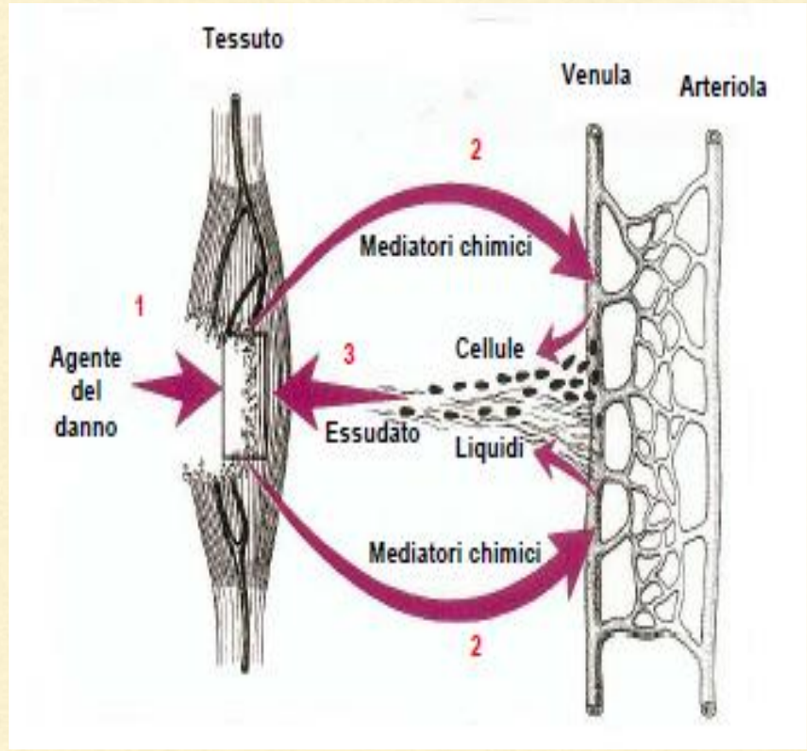
Mechanisms of Inflammation

The damaged tissue (1) releases chemical mediators (2) which diffuse towards sorrounding blood vessels, inducing:

- **Vessel reaction**
- **Tissue reaction**

…

rubor (redness), tumor (swelling)
calor (heat), dolor (pain),
functio laesa (altered function)

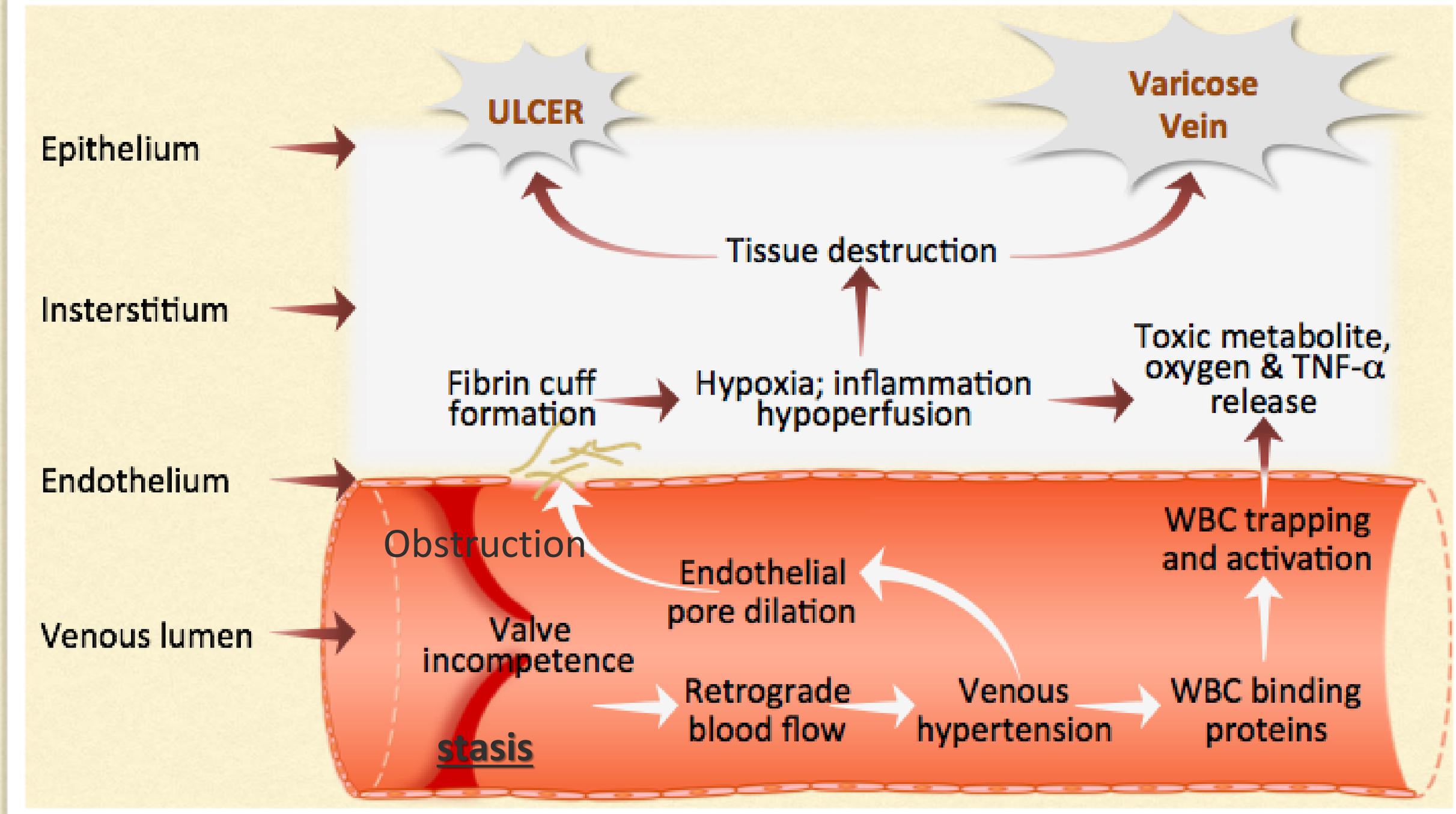


INFLAMMAGING

Chronic low grade cellular inflammation

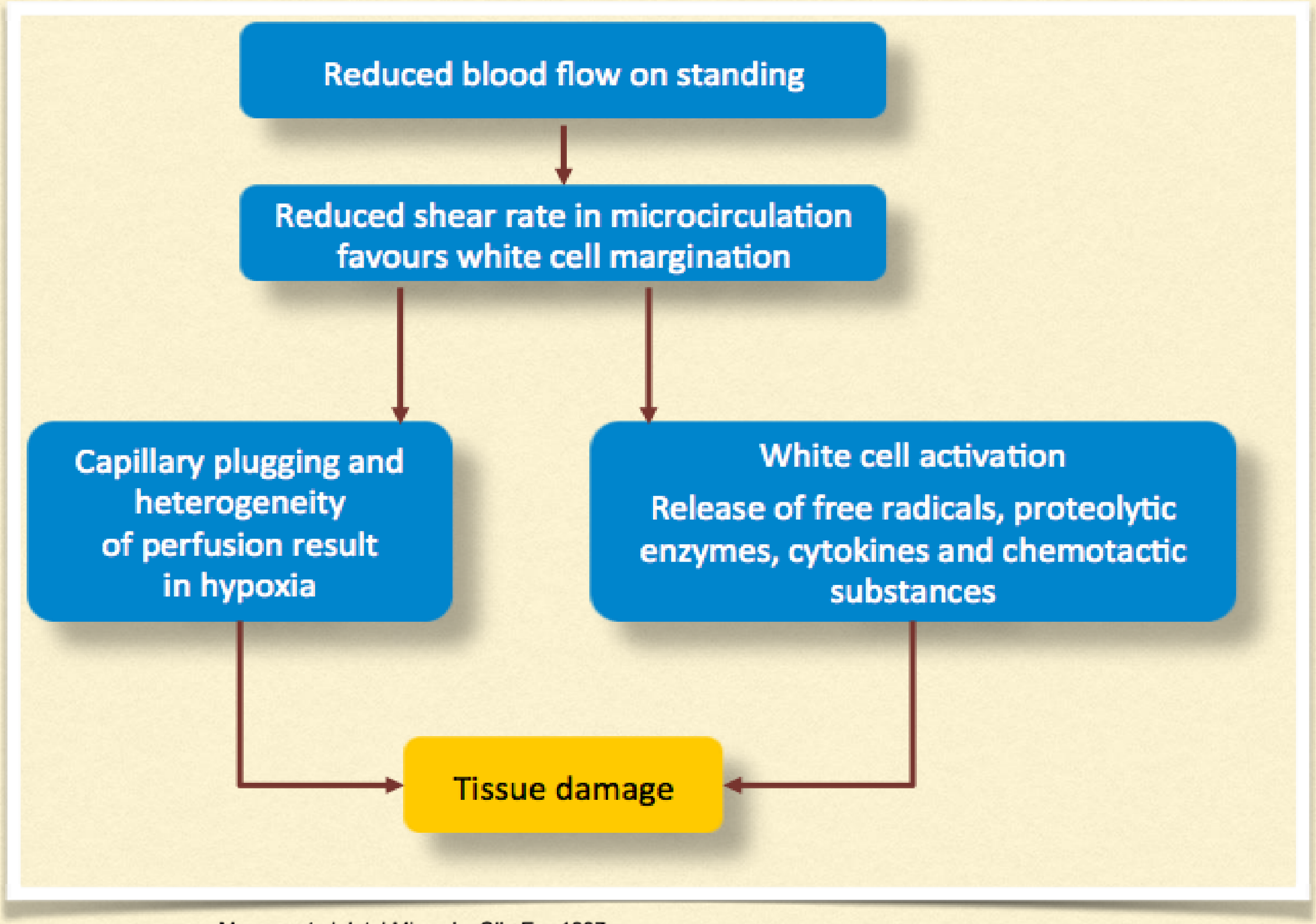
The root of all degenerative chronic diseases (and of venous and lymphatic diseases as well)

Progression of chronic venous disease



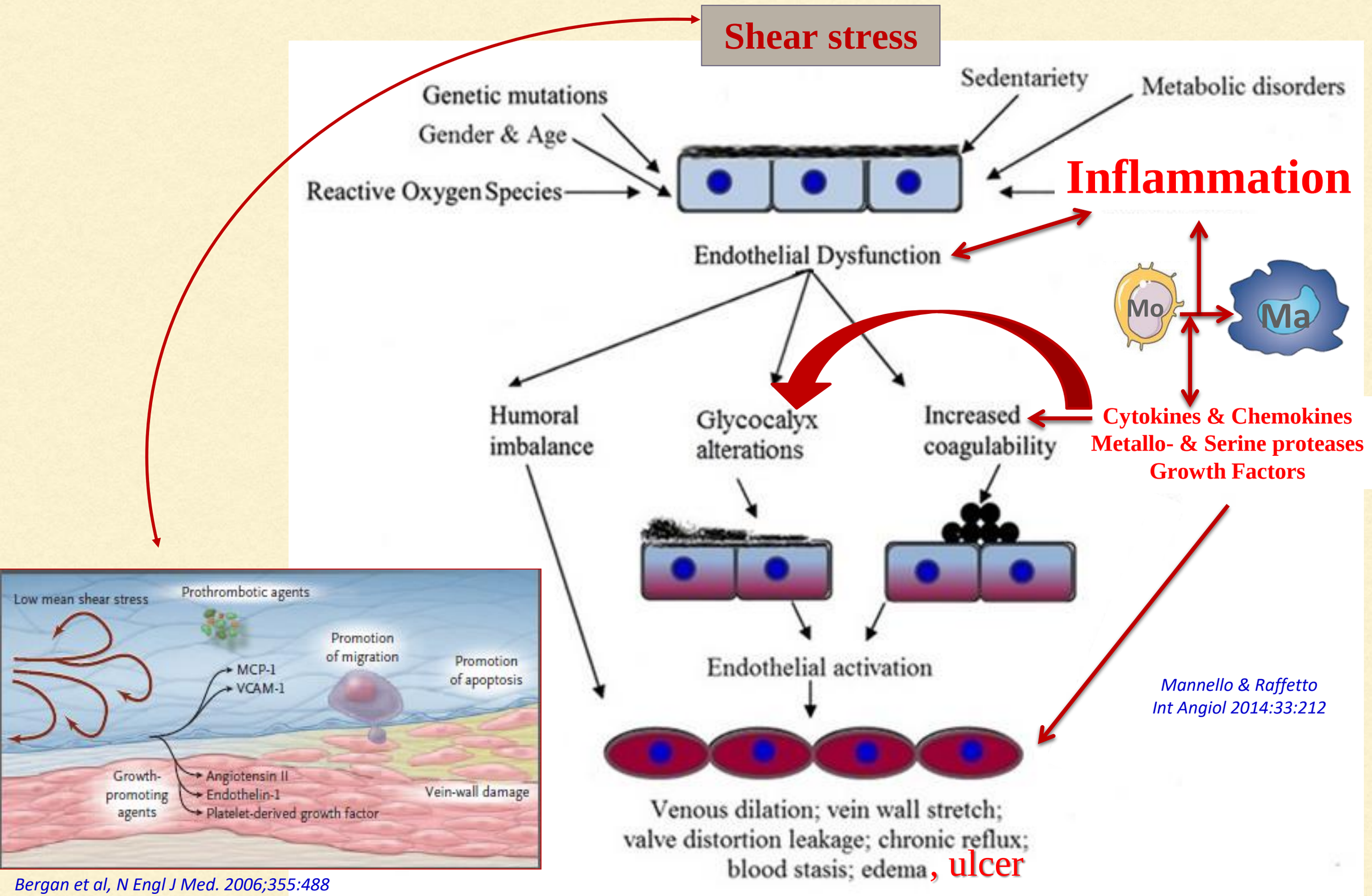
Adapted from Mannello & Raffetto, J Vasc Surg-Venous Lym Dis 2016

White cell trapping hypothesis



Moyses *et al, Int J Microcirc Clin Exp* 1987;

Hemodynamic & biomolecular stimuli in CVD/CVI



Mannello & Raffetto
Int Angiol 2014:33:212

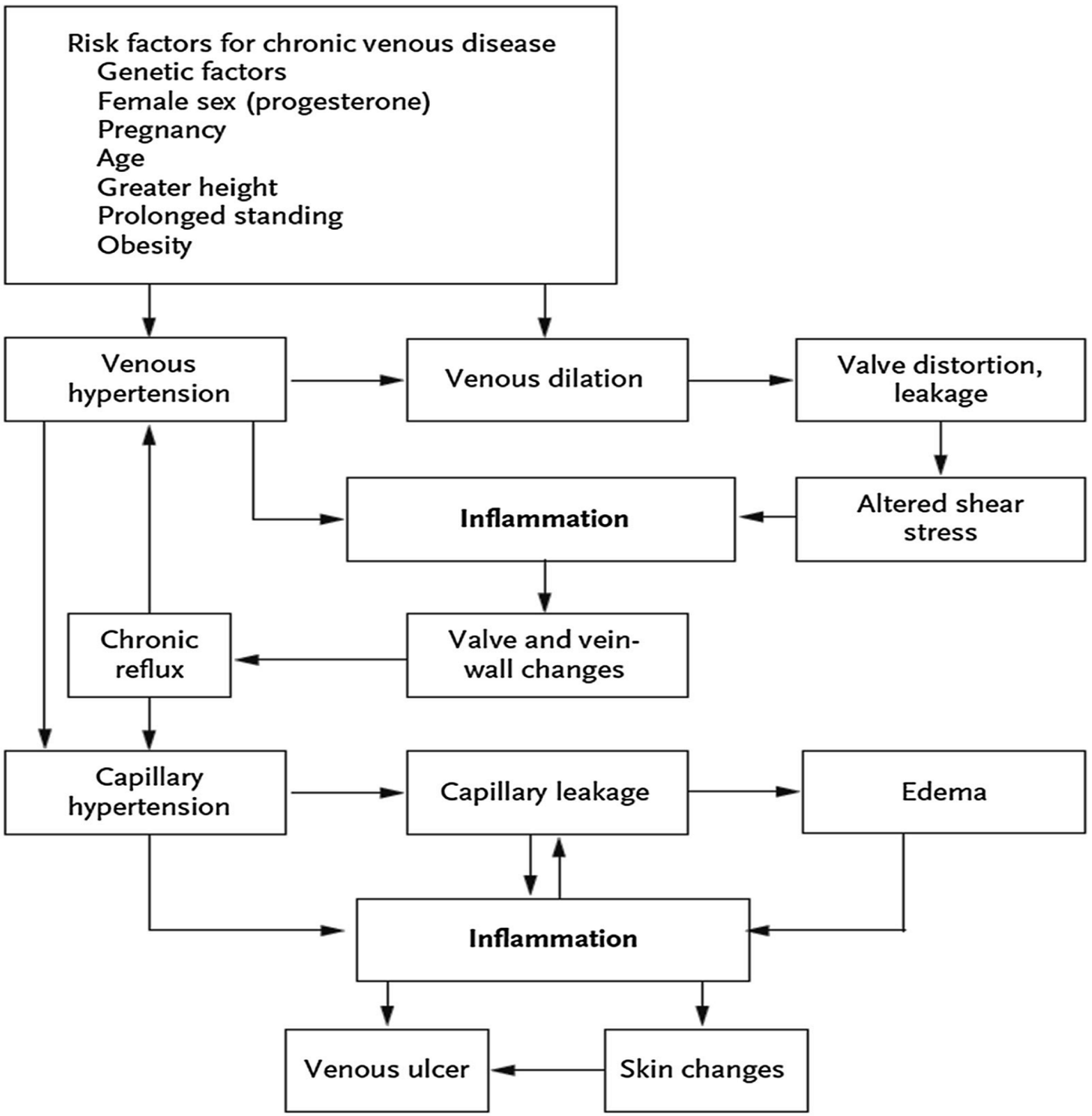
Bergan et al, N Engl J Med. 2006;355:488

Adv Ther (2019) 36:S13–S19
https://doi.org/10.1007/s12325-019-0885-3

REVIEW

How Does Chronic Venous Disease Progress from the First Symptoms to the Advanced Stages? A Review

Nicos Labropoulos



The Lymphatics and the Inflammatory Response: Lessons Learned from Human Lymphedema

Stanley G. Rockson. Lymphatic Research and Biology. September 2013, 11(3): 117-120

Am J Physiol Heart Circ Physiol 306: H1426–H1434, 2014.
First published March 14, 2014; doi:10.1152/ajpheart.01019.2013.

IL-6 regulates adipose deposition and homeostasis in lymphedema

Daniel A. Cuzzone,[1] Evan S. Weitman,[1] Nicholas J. Albano,[1] Swapna Ghanta,[1] Ira L. Savetsky,[1] Jason C. Gardenier,[1] Walter J. Joseph,[1] Jeremy S. Torrisi,[1] Jacqueline F. Bromberg,[2] Waldemar L. Olszewski,[3] Stanley G. Rockson,[4] and Babak J. Mehrara[1]

- **Excess plasma proteins as a cause of chronic inflammation and lymphoedema**: Quantitative electron microscopy March 1981:229–242 M. Gaffney, J. R. Casley-Smith

PLOS | ONE 2016

RESEARCH ARTICLE

Lipidomic Profiling of Adipose Tissue Reveals an Inflammatory Signature in Cancer-Related and Primary Lymphedema

Lisa M. Sedger[1¤]*, Dedreia L. Tull[2], Malcolm J. McConville[2], David P. De Souza[2], Thusitha W. T. Rupasinghe[2], Spencer J. Williams[2,3], Saravanan Dayalan[2], Daniel Lanzer[4], Helen Mackie[5], Thomas C. Lam[5], John Boyages[1,5]

Wound Rep Reg (2008) 16 642–648

Multiplexed analysis of matrix metalloproteinases in leg ulcer tissue of patients with chronic venous insufficiency before and after compression therapy

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Table2. MMP levels in ulcer tissue before and after 4 weeks of high-strength compression therapy (expressed as pg/µg of protein)

MMP	Pre-treatment ulcer (n=29)	Post-treatment percent ulcer (n=29)	Change (%)	p-value
MMP1	54.7±54.6	44.4±48.7	↓ 19	NS
MMP2	75.7±38	66.3±32	↓ 12	NS
MMP3	7.3±6.8	4.9±5.9	↓ 33	< 0.05
MMP7	0.66±0.67	0.60±0.8	↓ 13	NS
MMP8	184±131	120±120	↓ 34	< 0.05
MMP9	525±404	367±291	↓ 30	< 0.05
MMP12	0.15±0.17	0.14±0.26	↓ 2	NS
MMP13	4.5±6	5.0±4.5	↑ 11	NS

Percent Change, percent change in pretreatment MMP level after 4 weeks of compression treatment.
NS, not significant; MMP, matrix metalloproteinases.

Collagenase

Stromelysin

Neutrophil collagenase

Gelatinase B

Table 4. Gene expression of select MMP and inhibitors

Gene	Tissue type	Relative quotient† and SD
MMP1	Healthy	0.52
	Pretreatment ulcer	5,159 ± 2,060*
	Posttreatment ulcer	3,455 ± 761
MMP2	Healthy	0.75
	Pretreatment ulcer	21.9 ± 1.7
	Posttreatment ulcer	2.95 ± 0.09
MMP3	Healthy	1.93
	Pretreatment ulcer	2,257 ± 587*
	Posttreatment ulcer	1,113 ± 506
MMP8	Healthy	1.89
	Pretreatment ulcer	470 ± 249
	Posttreatment ulcer	256 ± 46
MMP9	Healthy	0.68
	Pretreatment ulcer	404 ± 163*
	Posttreatment ulcer	182 ± 32
TIMP1	Healthy	2.4
	Pretreatment ulcer	303 ± 251
	Posttreatment ulcer	50.3 ± 7.5
TIMP2	Healthy	1.1
	Pretreatment ulcer	11.7 ± 0.8
	Posttreatment ulcer	4.02 ± 0.07

… compression therapy results in a reduction of the pro-inflammatory environment characterizing chronic venous ulcers, and ulcer healing is associated with resolution of specific elevated levels of protease expression.

(J Vasc Surg 2009;49:1013-20.)

Inflammatory cytokine levels in chronic venous insufficiency ulcer tissue before and after compression therapy

Stephanie K. Beidler, MD, Christelle D. Douillet, PhD, Daniel F. Berndt, MS, Blair A. Keagy, MD, Preston B. Rich, MD, and William A. Marston, MD, *Chapel Hill, NC*

Table V: Cytokines demonstrating significant differences in ulcer tissue before compression compared to ulcer tissue after 4 weeks of compression therapy

		Before Therapy		After Therapy			
	Cytokines	Mean	(SE)	Mean	(SE)	F-Statistic	P-Value
Pro	IL-1α	0.89	(0.31)	0.28	(0.04)	4.40	0.045
Pro	IL-1β	0.17	(0.05)	0.03	(0.01)	8.54	0.007
Pro	IL-6	1.27	(0.31)	0.62	(0.15)	6.94	0.013
Chemokine	IL-8	15.18	(4)	3.80	(0.87)	7.06	0.013
Pro	IL-12p40	1.65	(0.31)	0.85	(0.14)	6.58	0.016
	G-CSF	0.27	(0.05)	0.14	(0.03)	4.63	0.04
CSF	GM-CSF	0.07	(0.01)	0.02	(0.01)	12.41	0.001
Pro	IFN-γ	0.27	(0.05)	0.14	(0.03)	8.94	0.006
Pro	TNF-α	0.02	(0.01)	0.01	(0)	4.18	0.05
GF	TGF-β1	0.24	(0.02)	0.34	(0.04)	5.14	0.031

(J Vasc Surg 2009;49:1013-20.)

Table VI : Cytokines displaying significantly different protein levels in rapid (healed > 40%) compared to delayed (healed < 40%) healers.

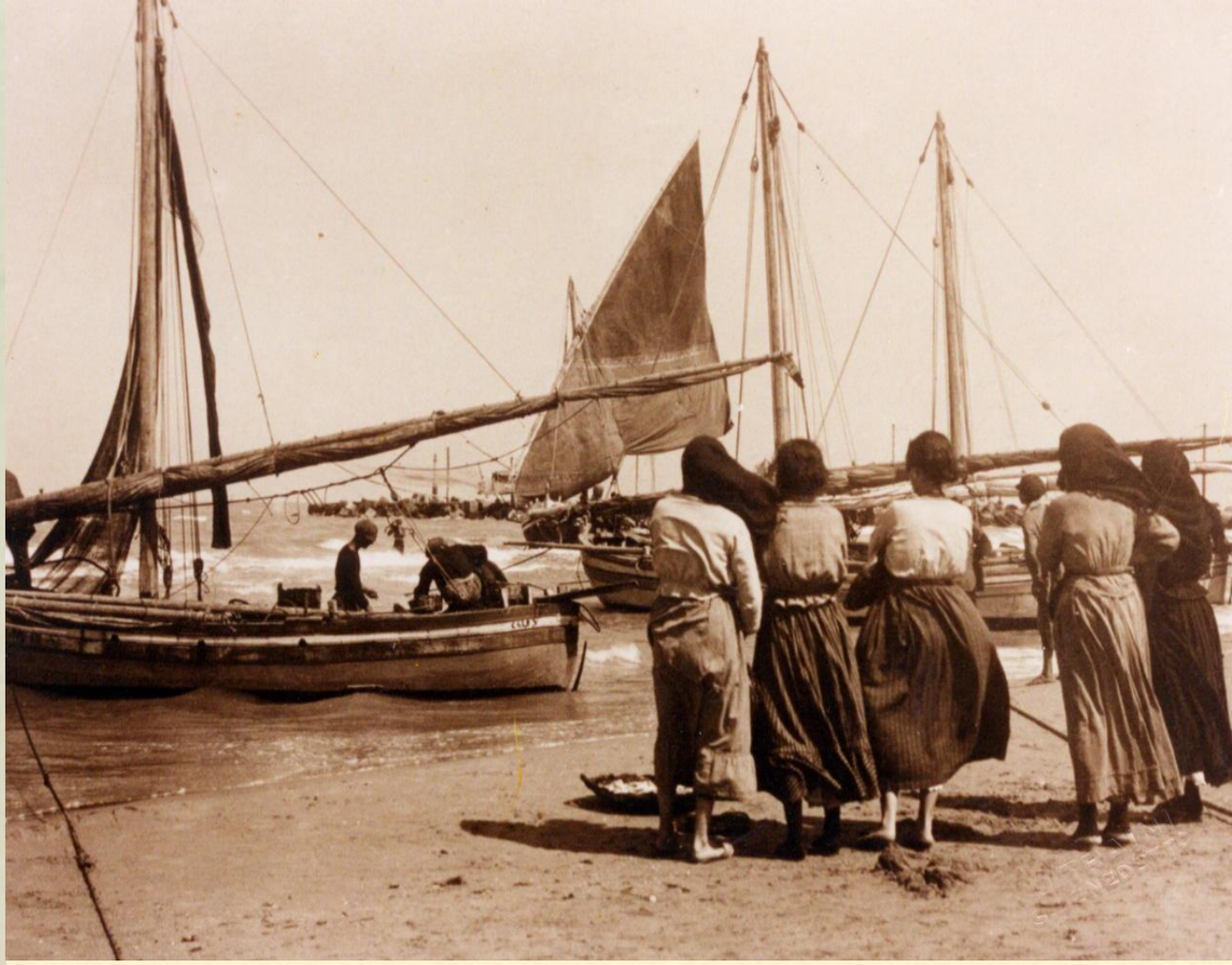
	Healed > 40%		Healed < 40%			
Cytokines	**Mean**	**SD**	**Mean**	**SD**	**Compression**	**P-Value**
IL-1α	1.43	2.3	0.35	0.30	Before	0.02
IL-1β	0.26	0.34	0.08	0.14	Before	0.03
IFN-γ	0.42	0.25	0.12	0.20	Before	0.001
IL-12p40	2.24	1.8	0.93	1.2	Before	0.01
GM-CSF	0.11	0.08	0.04	0.04	Before	0.02
IL-1 Ra*	25.3	18.6	15	13.5	After	0.02

CONCLUSION:

CVI ulcer healing is associated with a pro-inflammatory environment prior to treatment that reflects metabolically active peri-wound tissue which has the potential to heal. Treatment with compression therapy results in healing that is coupled with *reduced pro-inflammatory cytokine* levels and *higher levels of the anti-inflammatory cytokine*

Conclusions

- Several biophysical pathways (e.g. changes in shear stress and venous hypertension) lead to an inflammatory state which is typical of CVI
- Lymphedema IS a chronic inflammatory degenerative disease
- Compression therapy results in an improvement of CVI and lymphedema, which is an expression of peculiar modulation of inflammatory mediators and remodelling proteinases (the inflammatory cascade)



Thanks for your attention