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Deep vein thrombosis and inflammation, microcirculation, and influence of compression

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Disclosure

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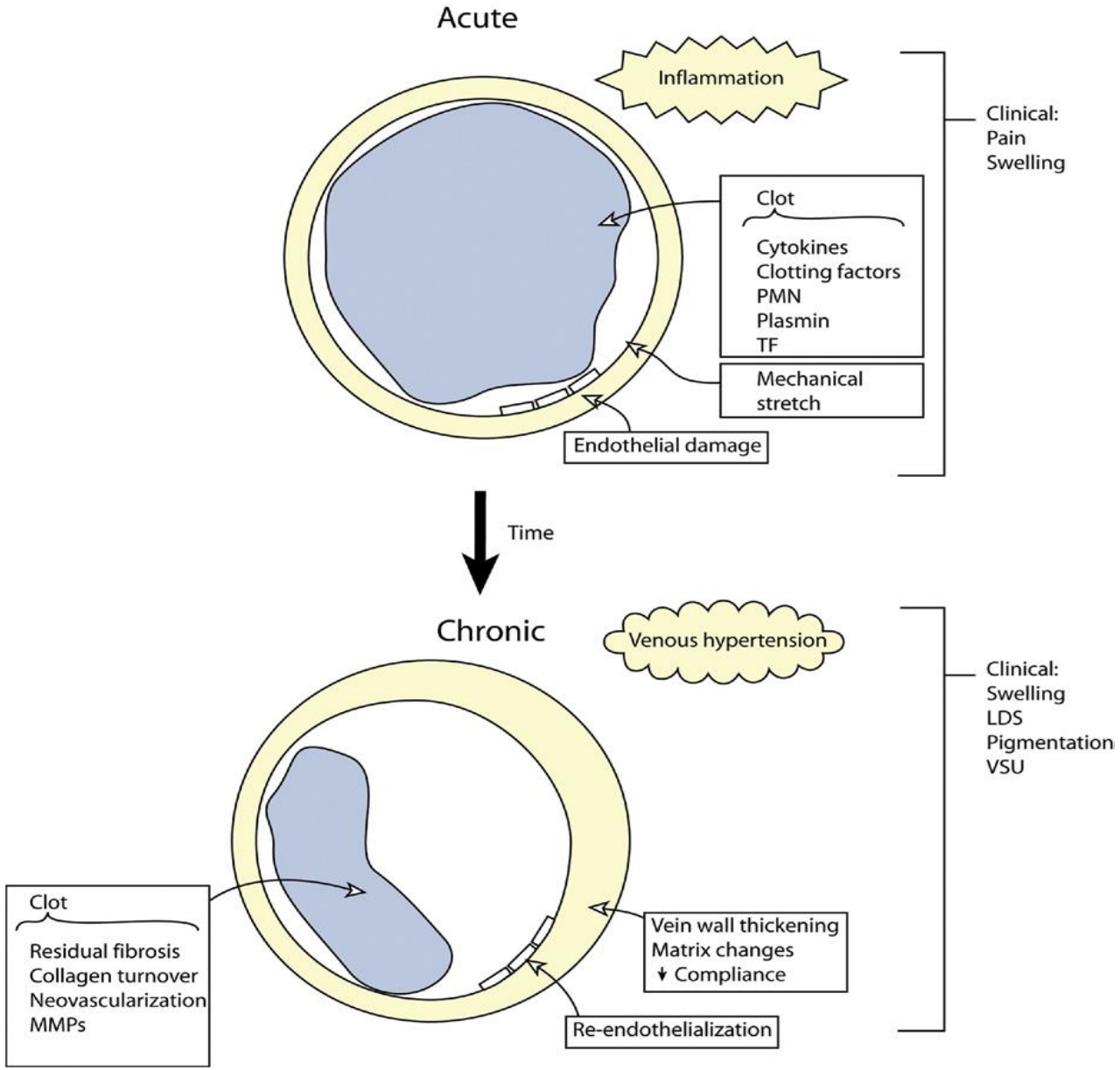
Financial disclosure:
I do not have any relevant financial relationships with any commercial interests

Unlabeled/unapproved uses disclosure:
I do not use any unlabeled or unapproved materials

Postthrombotic syndrome (PTS)

- Common late complication of acute DVT
  - Develops in almost half of all patients < 2 years, with severe symptoms, including venous ulceration, in 3%
- Occurs despite appropriate anticoagulation
  - PTS symptoms developed in 25-46% of patients after anticoagulation alone in the era of vitamin K antagonists
- Different PTS classifications
  - For assessment of PTS
    - Villalta scale
    - Ginsberg measure
    - Brandjes scale
  - For assessment of chronic venous insufficiency
    - CEAP classification
    - VCSS
    - Widmer

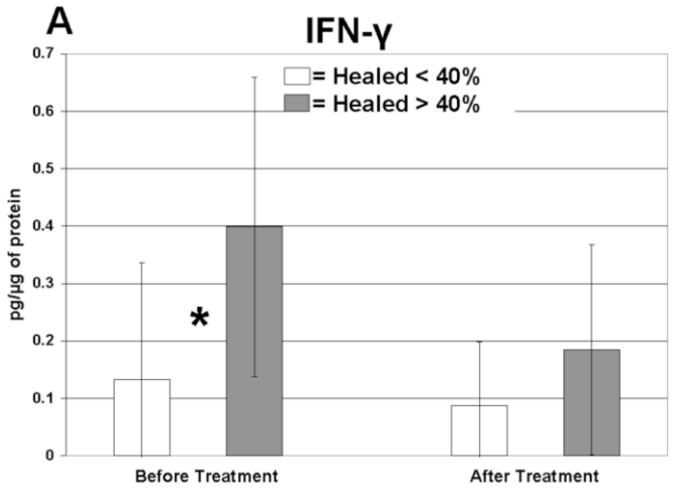
Pathophysiology of postthrombotic vein wall injury

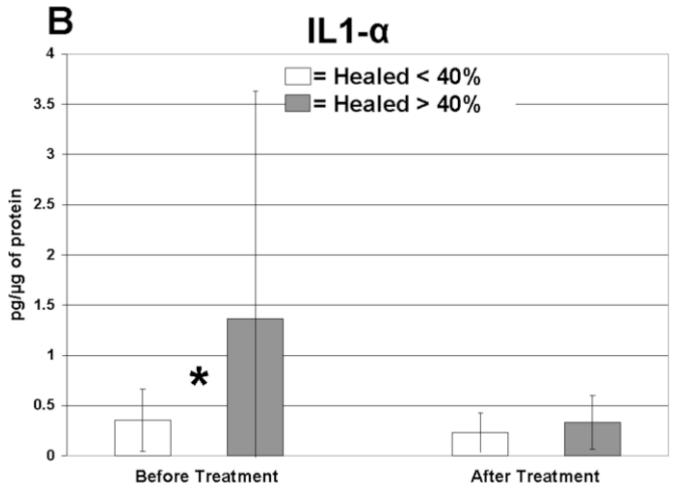


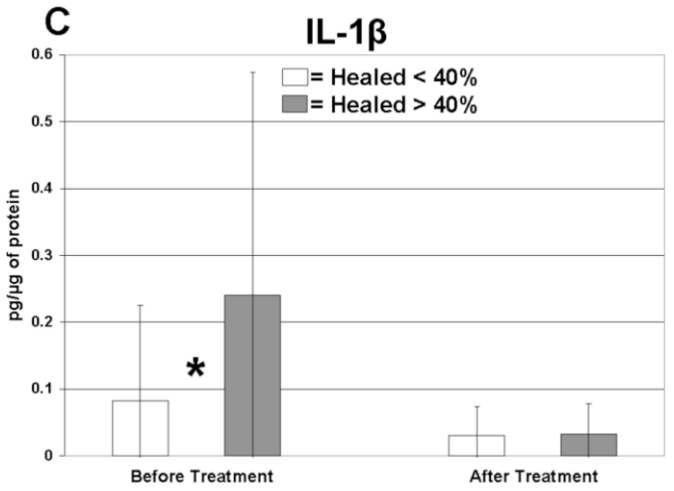
- Obstructive DVT is more injurious than perithrombus blood flow by promoting the inflammatory process.
- After DVT, mediators such as proteinases, growth factors, and cytokines released are likely the causal factor.
- Leukocytes may mediate release and activate matrix metalloproteinase 2 (MMP-2) and MMP-9, as well as promote vein wall fibrosis.
- The thrombus promotes vascular smooth muscle cell phenotypic change from a contractile to synthetic state, and the synthetic inflammatory vascular smooth muscle cell promotes collagen and other matrix accumulation and may increase vein wall fibrosis and stiffness.

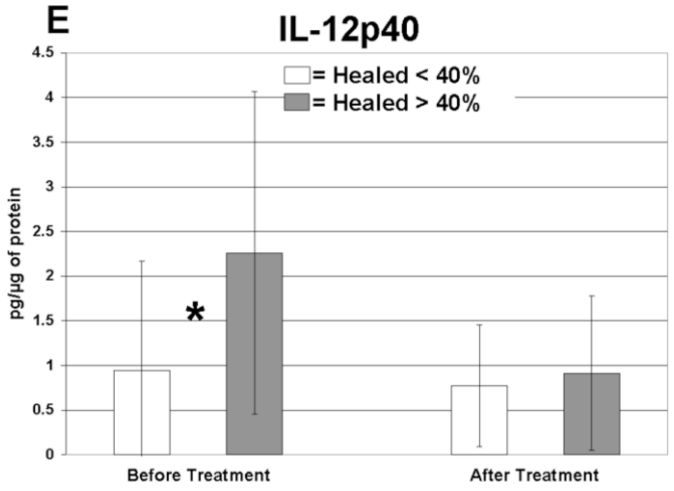
Henke P et al. ***J Vasc Surg*** 2011; 53: 500-9

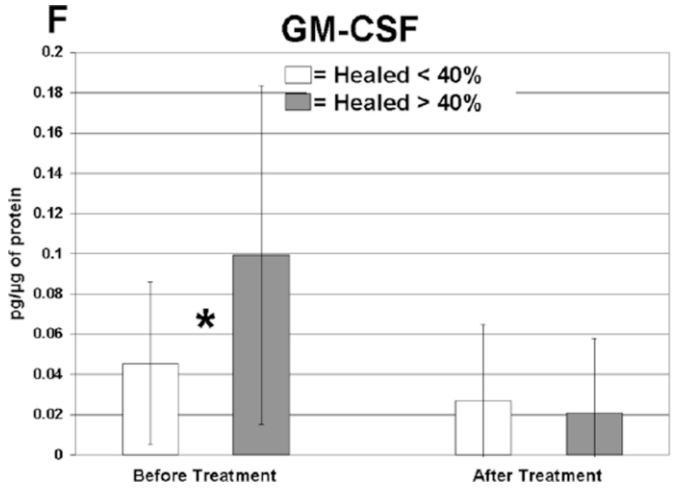
Inflammatory cytokine levels in CVU before and after compression therapy

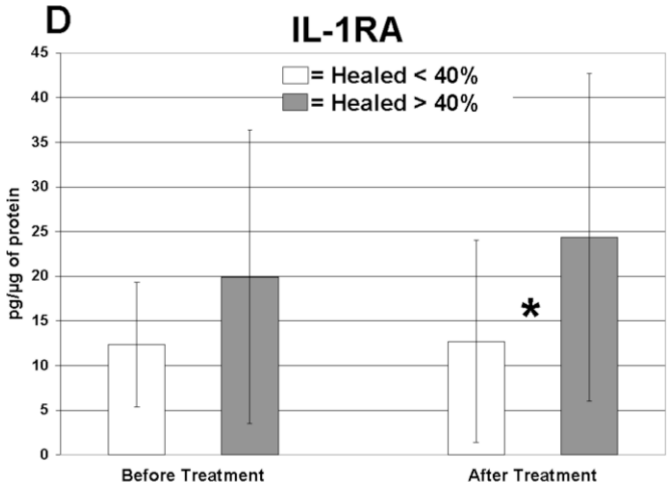








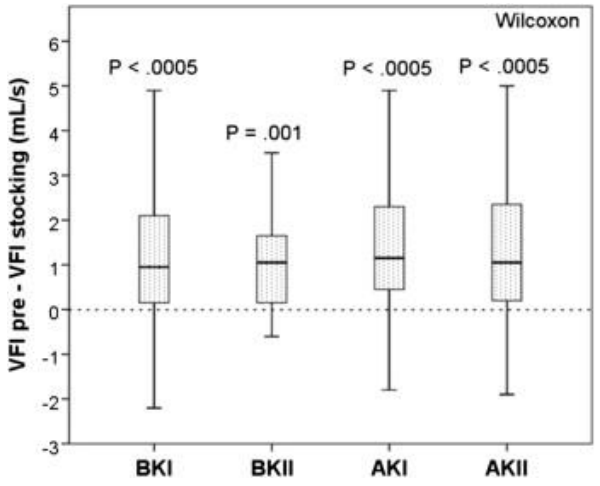


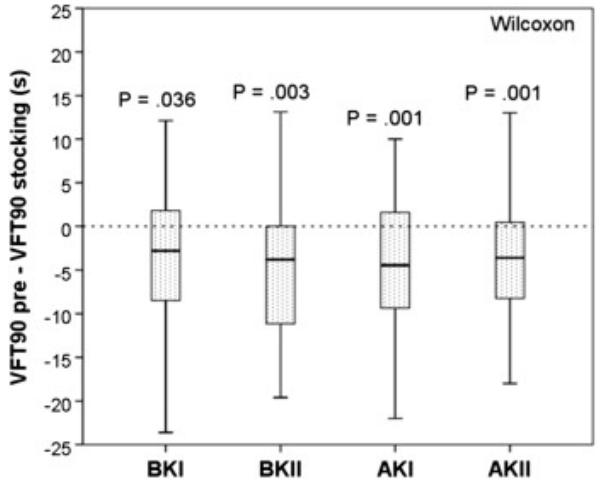


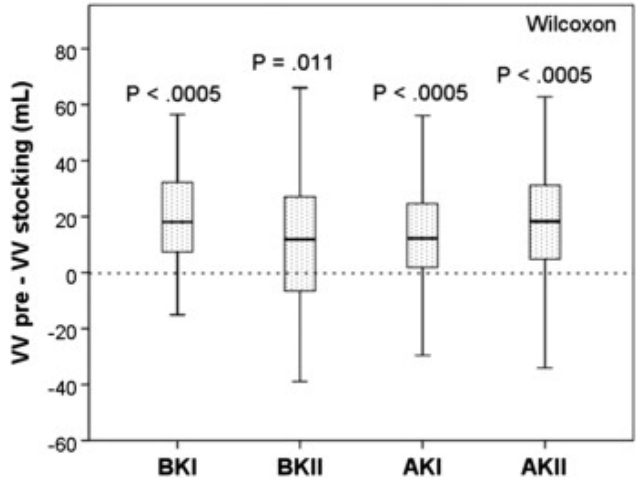
* = statistically significant with P < 0.05

Beidler SK et al. ***J Vasc Surg*** 2009; 49: 1013-20

GCS significantly improve hemodynamic performance in PTS



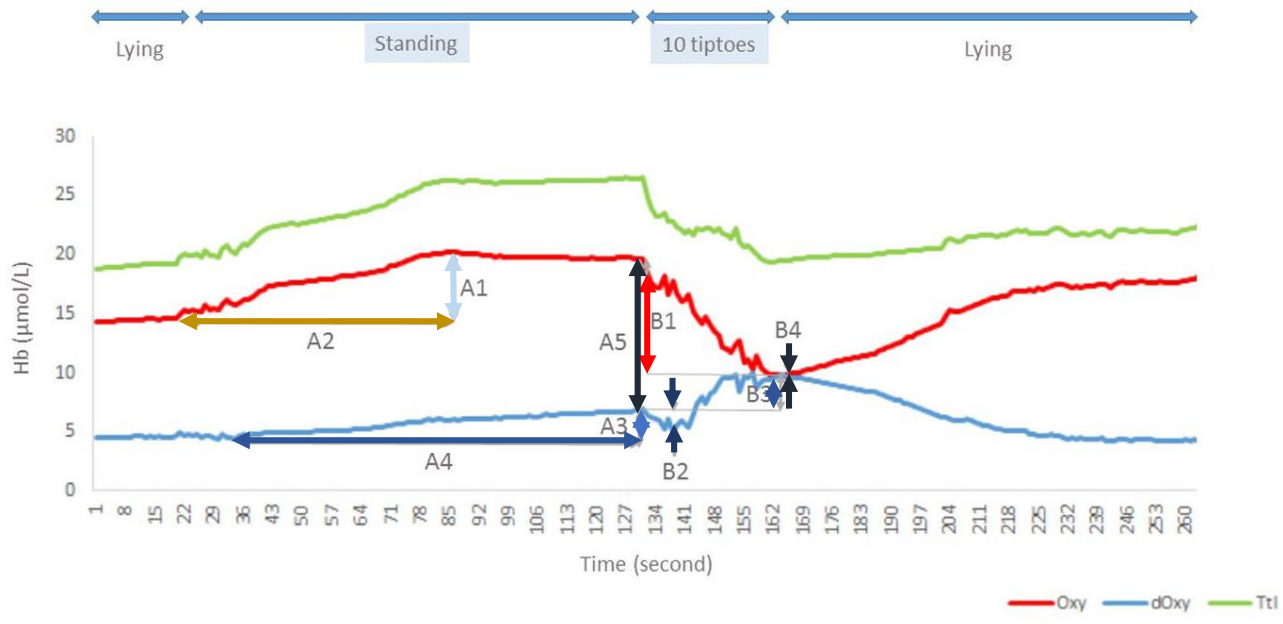


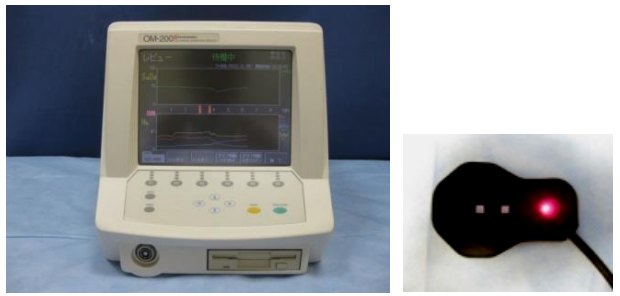


	VFI improvement	*r* value (Spearman rho test)	P-value (Spearman rho test)
Class I (18-21 mm Hg)	1.10 (0.3-2.18)	.420	<.0005
Class II (23-32 mm Hg)	1.05 (0.2-2.08)	.350	.001
Below knee	1.0 (0.13-2.08)	.327	.003
Above knee (thigh-length)	1.10 (0.4-2.38)	.452	<.0005
All stockings summary	1.10 (0.2-2.10)	.390	<.0005

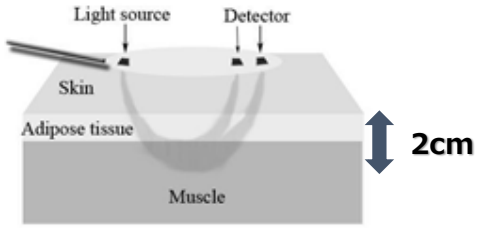
Lattimer CR et al. ***J Vasc Surg*** 2013; 58: 158-65

Measurements of changes in calf muscle oxygenation in patients with CVD using near-infrared spectroscopy (NIRS)





OM-200 (Shimazu Co, JAPAN)



Standing

A1. Maximum increase in O_2Hb on standing (ΔO_2Hb_{st})
A2. Time elapsed until the maximum increase in O_2Hb ($_TO_2Hb_{st}$)
A3. Maximum increase in HHb on standing (ΔHHb_{st})
A4. Time elapsed until the maximum increase in HHb ($_THHb_{st}$)
A5. Oxygen index at the end of standing (HbD_{st})

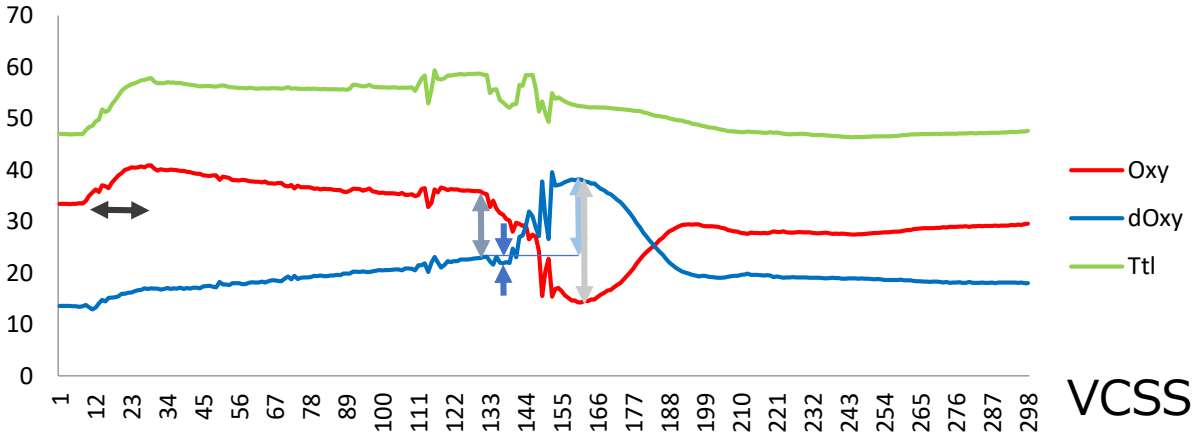
10 tiptoes

B1. Maximum decrease in O_2Hb during exercise (ΔO_2Hb_{ex})
B2. Venous expulsion during exercise ($\Delta HHbE_{ex}$)
B3. Venous retention during exercise ($\Delta HHbR_{ex}$)
B4. Oxygen index at the end of exercise (HbD_{ex})

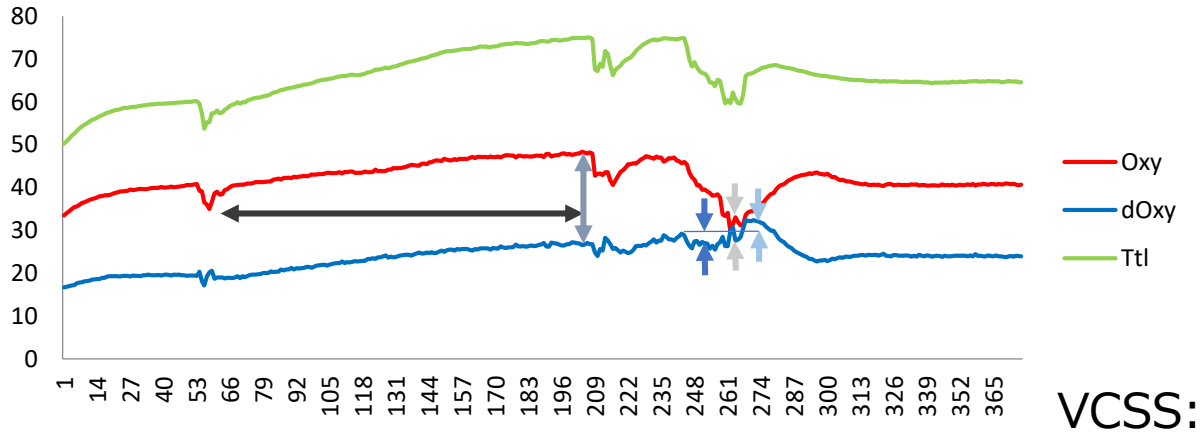
Oxygen index: $HbD = O_2Hb - HHb$

Yamaki T et al. ***J Vasc Surg Venous Lymphat Disord*** 2013;1:333-40

NIRS-derived parameters between patients with and without PTS



VCSS: 22



VCSS: 5

Standing

Variable	PTS n = 21 patients	No PTS n = 22 patients	*P*-value*
On standing			
ΔO_2Hb_{st} (µmol/L)	11 ± 19	11 ± 6	0.131
ΔHHb_{st} (µmol/L)	9 ± 11	7 ± 3	0.876
HbD_{st} (µmol/L)	12 ± 8	22 ± 11	0.001
${}_TO_2Hb_{st}$ (s)	43 ± 41	107 ± 58	0.001

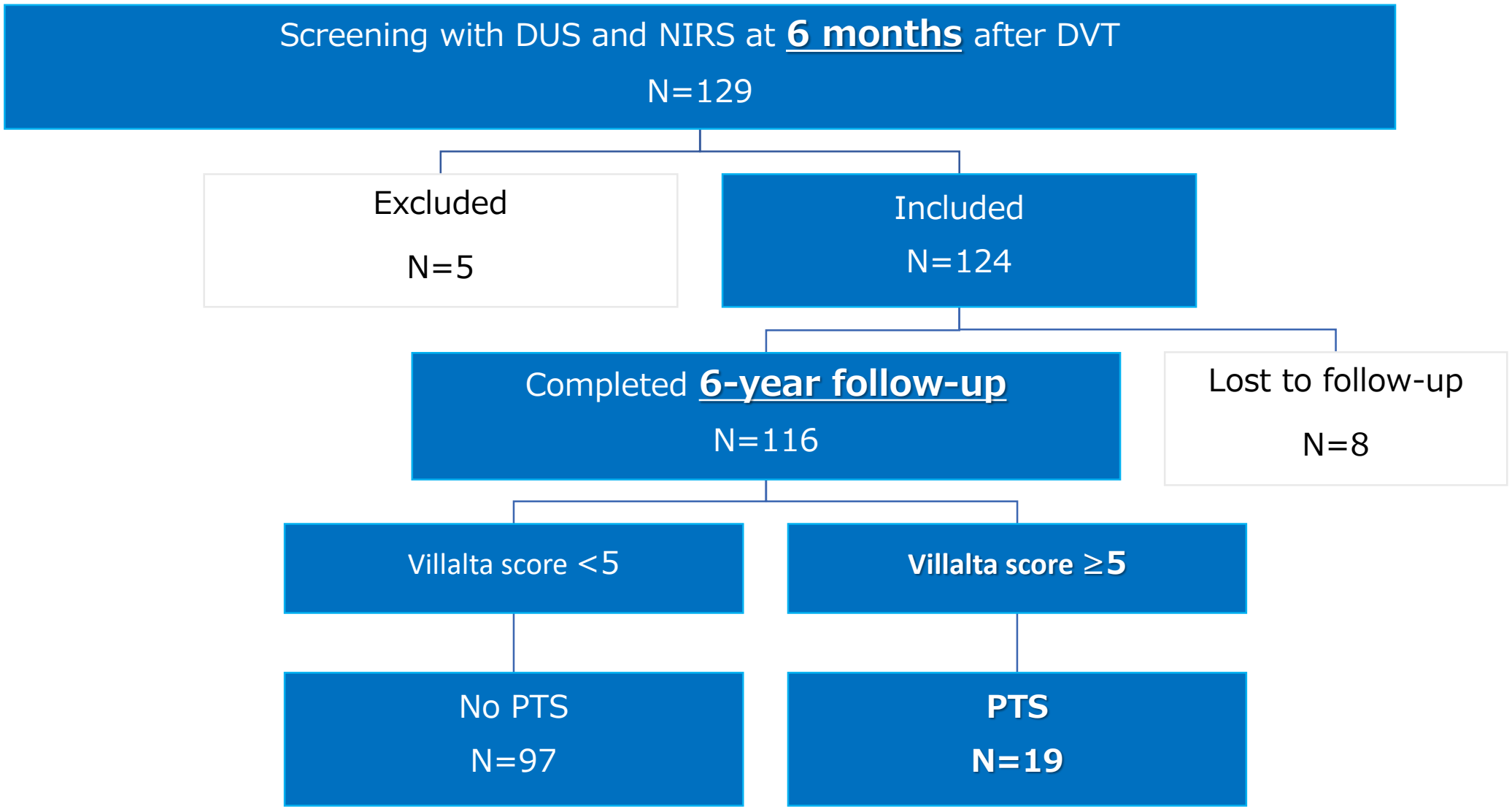
10 tiptoes

Variable	PTS n = 21 patients	No PTS n = 22 patients	*P*-value*
ΔO_2Hb_{ex} (µmol/L)	-14 ± 11	-10 ± 5	0.083
$\Delta HHbE_{ex}$ (µmol/L)	-2 ± 1	-3 ± 3	0.016
$\Delta HHbR_{ex}$ (µmol/L)	8 ± 7	3 ± 2	0.001
HbD_{ex} (µmol/L)	-10 ± 16	10 ± 10	<0.001

* Wilcoxon non-parametric rank sum test. Values expressed as mean ± SD.

Yamaki T et al. ***J Vasc Surg Venous Lymphat Disord*** 2014;2:424-32

Study flow diagram



Yamaki T et al. ***J Vasc Surg Venous Lymphat Disord*** 2016;4:446-54

Patients' characteristics compared between patients with and without PTS

	No PTS n = 97	PTS n = 19	P-value
Characteristics at initial visit			
Age (years)	61.3 ± 18.3	57.2 ± 15.5	0.273
Male gender, no (%)	32 (33.0)	10 (52.6)	0.103
Body mass index (kg m ^{2})	22.6 ± 3.1	25.2 ± 2.3	0.343
Duration of anticoagulation (months)	18.1 ± 28.2	18.9 ± 14.7	0.899
Risk factors, no (%)			
Active cancer	14 (14.4)	1 (5.3)	0.276
Congenital heart failure	1 (1.0)	0 (0)	0.657
Hormone replacement therapy	12 (12.4)	4 (21.1)	0.316
Immobilization	12 (12.4)	0 (0)	0.105
Renal failure	5 (5.2)	2 (10.5)	0.369
Surgery	40 (41.2)	5 (26.3)	0.222
Stroke	2 (2.1)	2 (10.5)	0.064
Idiopathic DVT	**12 (12.4)**	**7 (36.8)**	**0.008**
Distribution of DVT, no (%)			
Ilio-femoral DVT	**14 (14.4)**	**8 (42.1)**	**0.005**
Femoro-popliteal DVT	32 (33.0)	10 (52.6)	0.103
Calf DVT	51 (52.6)	1 (5.3)	<0.0001
Venous abnormality at 6 month, no (%)			
No abnormalities	52 (53.6)	1 (5.2)	<0.0001
Obstruction	16 (16.5)	5 (26.3)	0.309
Reflux	12 (12.4)	4 (21.1)	0.316
Obstruction and reflux	**17 (17.5)**	**9 (47.4)**	**0.004**

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NIRS-derived parameters compared between patients with and without PTS at 6 months

	PTS n = 19	No PTS n = 97	p-value
On standing			
ΔO_2Hb_{st} (µmol/L)	8.4 ± 5.5	10.6 ± 9.9	0.438
ΔHHb_{st} (µmol/L)	10.5 ± 10.4	14.4 ± 6.7	0.180
HbD_{st} (µmol/L)	12.8 ± 13.5	10.3 ± 14.8	0.609
$_TO_2Hb_{st}$ (seconds)	**37.6 ± 32.7**	**62.9 ± 35.0**	**0.039**
$_THHb_{st}$ (seconds)	190.4 ± 73.3	209.9 ± 59.4	0.382
During exercise			
ΔO_2Hb_{ex} (µmol/L)	-14.8 ± 10.1	-11.2 ± 6.9	0.216
$\Delta HHbE_{ex}$ (µmol/L)	**-3.4 ± 3.9**	**-5.8 ± 2.6**	**0.040**
$\Delta HHbR_{ex}$ (µmol/L)	8.1 ± 8.6	5.9 ± 3.4	0.281
HbD_{ex} (µmol/L)	-6.2 ± 24.7	-5.3 ± 13.7	0.908

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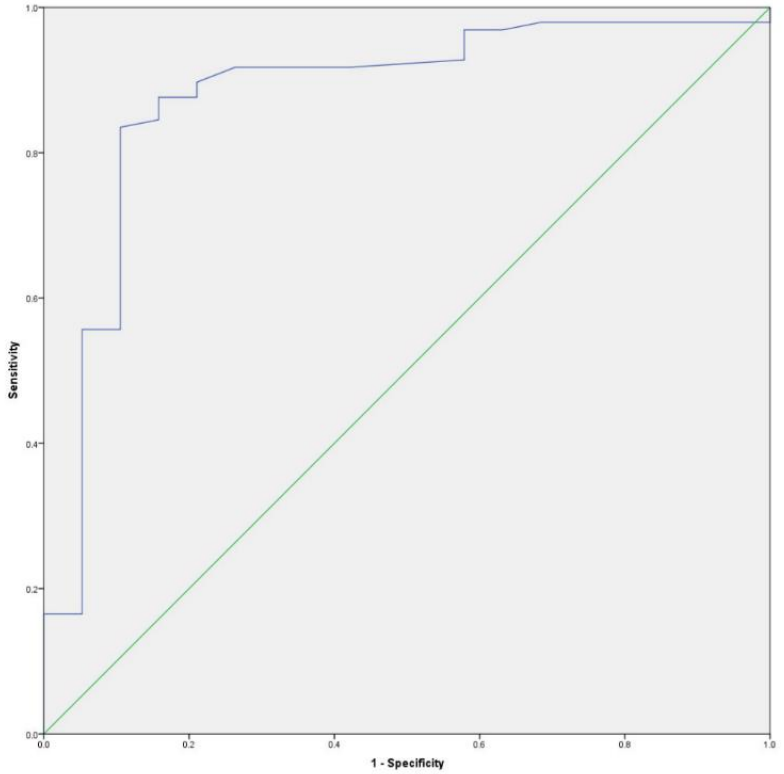
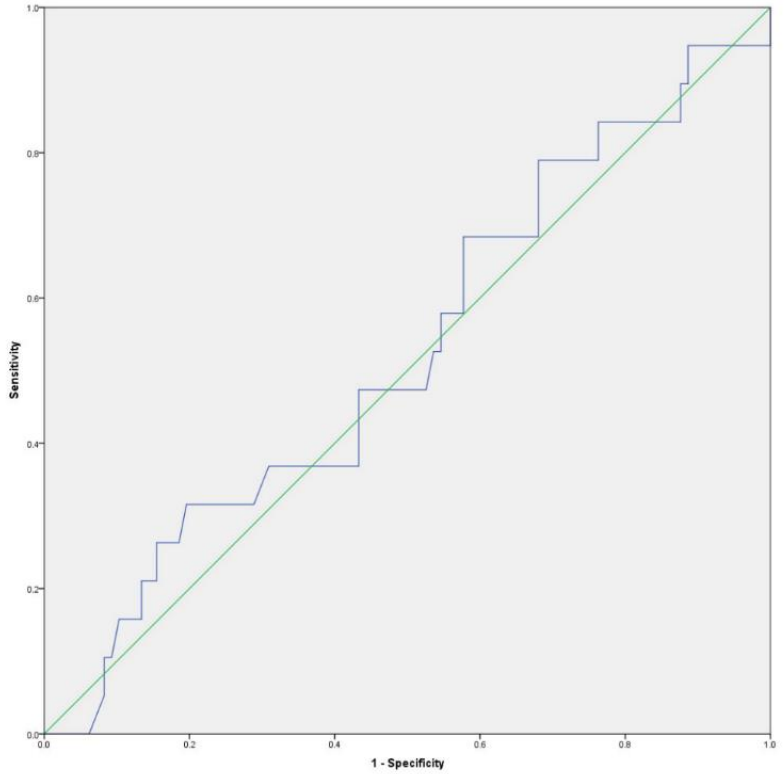
Ability of NIRS-derived confounding parameters to predict PTS



Cut off: $_{T}O_2Hb_{st} \leq 48$ seconds
AUC 0.88, 95% CI, 0.80-0.93, p<0.0001 with a sensitivity of 89.5% and a specificity of 83.5%.



Cut-off: $\Delta HHbE_{ex} > -0.87$ µmol/L
AUC 0.53, 95% CI 0.43-0.62, p=0.732 with a sensitivity of 31.6% and a specificity of 80.4%.

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Univariate analysis to evaluate potential predictors of PTS (p<0.1)

Variable	OR	95% CI	p-value
Variables at initial visit			
Risk factors for DVT			
Stroke	5.59	0.74-42.41	0.064
Idiopathic DVT	4.13	1.36-12.55	0.008
Distribution of DVT			
Ilio-femoral DVT	4.31	1.48-12.60	0.005
Variables at 6-month			
Venous abnormalities			
Obstruction and reflux	4.24	1.50-12.00	0.004
NIRS-derived parameters			
$_{T}O2Hb_{st}$ ≤48 seconds	43.03	9.04-204.81	<0.001

Yamaki T et al. ***J Vasc Surg Venous Lymphat Disord*** 2016;4:446-54

Multivariate logistic regression analysis to evaluate potential predictors of PTS

Variable	β	Wald	OR	95% CI	p-value
Stroke	1.00	0.31	2.73	0.08-92.63	0.577
Idiopathic DVT	-0.02	0.01	0.98	0.16-5.99	0.980
Ilio-femoral DVT	1.40	2.45	4.07	0.02-23.63	0.118
Obstruction and reflux	**1.57**	**4.00**	**4.81**	**10.3-22.36**	**0.045**
$_{T}O2Hb_{st}$ ≤48 seconds	**3.98**	**17.78**	**53.73**	**8.43-342.41**	**<0.001**

Yamaki T et al. ***J Vasc Surg Venous Lymphat Disord*** 2016;4:446-54

Acute effect of GCS on calf muscle oxygenation

–Initial pilot study with 13 CVI patients–

	No GCS	Class I (18-21 mm Hg)	Class II (23-32 mm Hg)	P-value*
	N=13			
Standing				
ΔO_2Hb_{st} (μmol/L)	21.3 ± 19.9	19.6 ± 21.6	21.7 ± 19.3	0.962
ΔHHb_{st} (μmol/L)	15.8 ± 14.7	17.0 ± 16.9	16.0 ± 14.7	0.976
HbD_{st} (μmol/L)	18.7 ± 12.2	14.8 ± 10.9	17.8 ± 10.9	0.656
$_TO_2Hb_{st}$ (s)	26.5 ± 14.3	46.8 ± 49.6	58.5± 57.5	0.194
$_THHb_{st}$ (s)	132.5 ± 34.7	141.4 ± 24.5	14.5± 35.3	0.573
10 tiptoes				
ΔO_2Hb_{ex} (μmol/L)	-23.6 ± 19.7	-24.0 ± 19.1	-24.4 ± 19.5	0.994
$\Delta HHbE_{ex}$ (μmol/L)	-7.5 ± 8.0	-9.9 ± 9.9	-9.8 ± 10.1	0.760
$\Delta HHbR_{ex}$ (μmol/L)	11.9 ± 13.4	9.8 ± 10.9	5.7 ± 9.2	0.370
HbD_{ex} (μmol/L)	-12.8 ± 22.9	-11.2 ± 19.3	-5.7± 21.9	0.680

*One-way analysis of variance (ANOVA)

Yamaki T. ***Unpublished data***

Conclusions

- The vascular inflammatory response involves complex interaction between inflammatory cells (neutrophils, lymphocytes, monocytes, macrophages), endothelial cells (ECs), vascular smooth muscle cells (VSMCs), and extracellular matrix (ECM).
- Persistent increase in cytokines are associated with venous hypertension.
- Use of compression stockings decreases pro-inflammatory and increases anti-inflammatory cytokines by reducing venous hypertension.
- Use of compression stockings improves global venous hemodynamics.
- Although, there are no meaningful results obtained at this moment, compression stockings may have positive effects on calf muscle microcirculation.