INTRAVENOUS IRON ADMINISTRATION AND EARLY ATHEROGESESIS, IS ACTUALLY IRON SUCROSE RESPONSIBLE?

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BACKGROUND

•Recently the association between i.v. iron sucrose (IS) administration and accelerated atherogenesis has been suggested in one report (J Am Soc Nephrol JASN 2014; 25:2596-606).

•However, since the study was performed using an IS similar (ISS), namely "Fe-Back", and taking into account that the same ISS "Fe-Back" was already linked to significant inflammatory response in different tissues (Inflamm Allergy Drug Targets. 2012; 11: 66-78), the precise mechanism by which vascular damage may occur remains unclear.

OBJECTIVE

To clarify whether the original Iron Sucrose (IS) administration by itself, actually induces vascular damage in normal rats.

METHODS

Three groups of Sprague Dawley rats received an i.v. dose of 40 mg iron/kg bw as originator IS (G1) or ISS (G2) on days 0, 7, 14, 21 and 28.
A control group with saline was also included G3 (control). All animals were sacrificed on day 29. Homogenates of aorta (Ao) and mesenteric arteries (MA) were prepared and biological parameters evaluated such as malondialdehyde (MDA) content, reduced glutathione / oxidized glutathione (GSH/ GSSG) ratio and glutathione peroxidase activity (GPx).
Concentrations of tissue nitrotyrosine (a marker for nitrosative stress) eNOS, VCAM-1 and IL-6 (markers for vascular damage) were assessed by immunohistochemistry.

RESULTS

- No differences were observed between G1 and G2 on Hb.
- TSAT and serum iron were both significantly ($p<0.01$) increased in G2 vs. G1.

Table 1. Evaluation of Oxidative stress in tissue homogenates.

Mean SD	G1 IS (n= 8)	G2 ISS (n= 8)	G3 (Control) (n=8)
MDA (mM/mg prot)			
a) Ao	3.3 ± 0.4	13.7 ± 0.9*	2.9 ± 0.5
b) MA	3.4 ± 0.5	14.1 ± 1.1*	3.0 ± 0.3
GSH/GSSG ratio			
a) Ao	6.1.± 0.6	3.8 ± 0.3*	6.8 ± 0.5
b) MA	5.9 ± 0.5	3.5 ± 0.2*	6.6 ± 0.4
GPx (U/mg prot)			
a) Ao	296.3 ± 25.8	386.4 ± 21. 1*	275.8 ± 20.2
b) MA	311.9 ± 17.9	394.0 ± 24.0*	300.6 ± 11.7

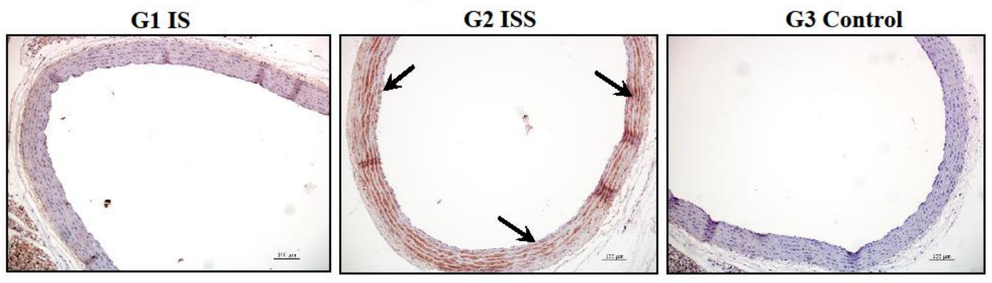
* p< 0.01 versus G1 and G3

Table 2. Immunostaining in Aorta and Mesenteric Artery.

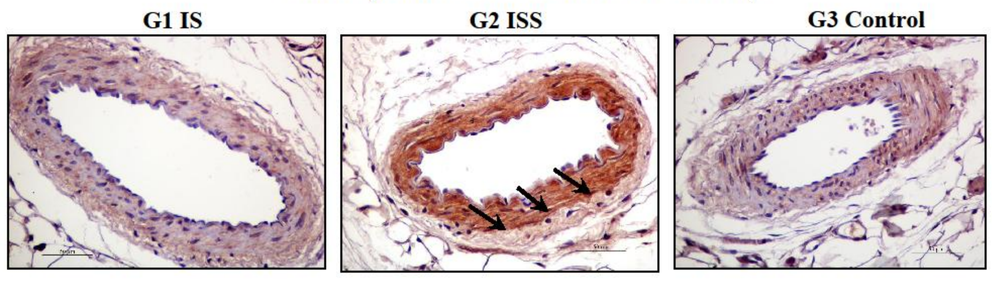
Mean SD	G1 IS (n= 8)	G2 ISS (n= 8)	G3 (Control) (n=8)
NT (% staining)			
a) Ao	1.1 ± 0.4	9.0 ± 1.3*	0.9 ± 0.3
b) MA	1.3 ± 0.5	9.3 ± 2.0*	1.1 ± 0.4
IL6 (% staining)			
a) Ao	1.8 ± 0.4	8.6 ± 2.3*	1.4 ± 0.3
b) MA	2.0 ± 0.3	10.5 ± 2.5*	1.8 ± 0.3
VCAM (% staining)			
a) Ao	1.4 ± 0.5	6.9 ± 1.2*	1.1 ± 0.4
b) MA	1.5 ± 0.6	7.3 ± 1.1*	1.2 ± 0.3
eNOS (% staining)			
a) Ao	2.3 ± 0.6	0.8 ± 0.4*	2.7 ± 0.7
b) MA	2.9 ± 0.3	0.6 ± 0.2*	3.0 ± 0.4

* p< 0.01 versus G1 and G3

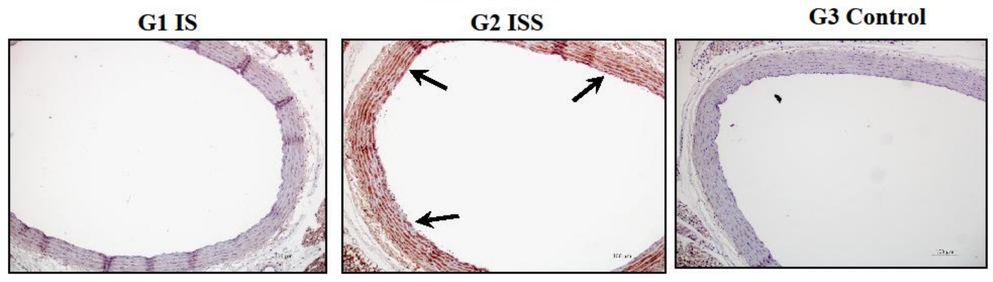
Nitrotyrosine in Aorta



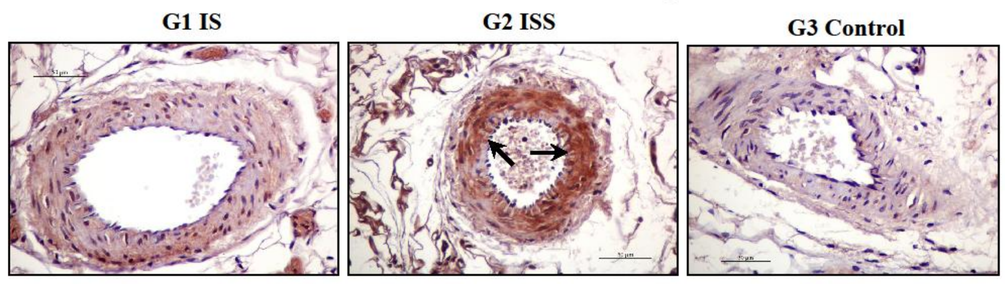
Nitrotyrosine in Mesenteric Artery



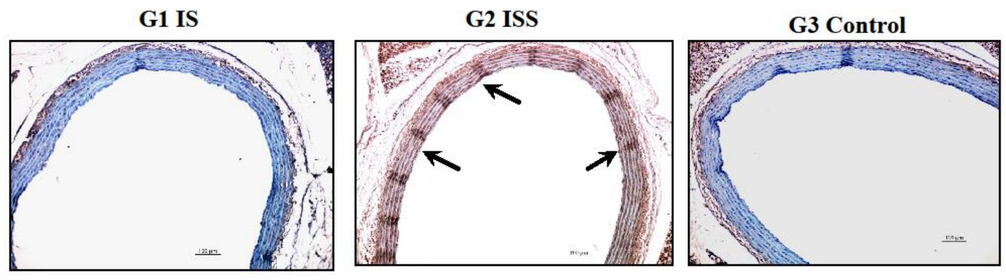
IL6 in Aorta



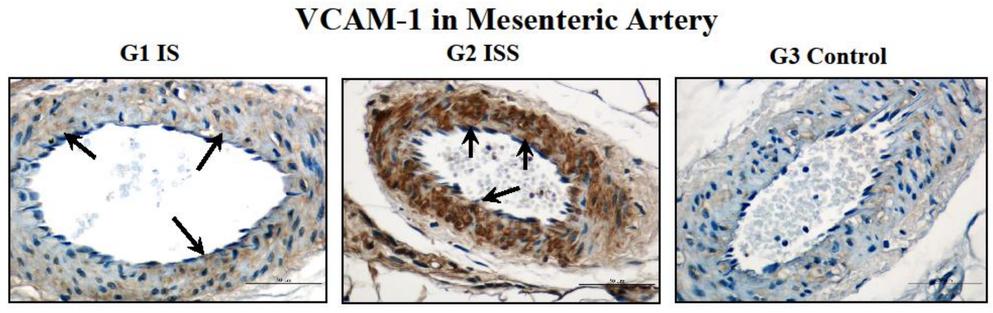
IL6 in Mesenteric Artery



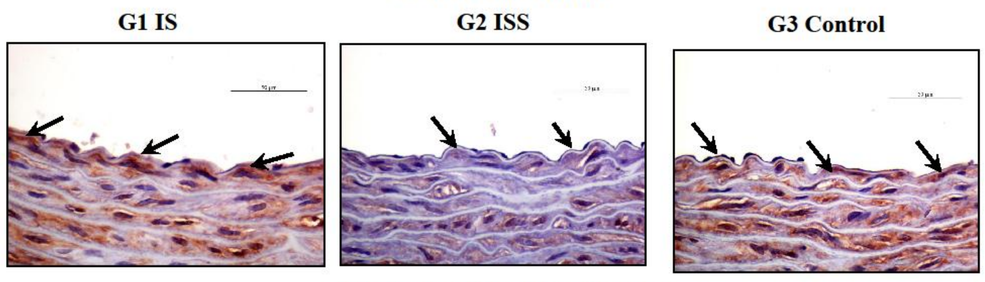
VCAM-1 in Aorta



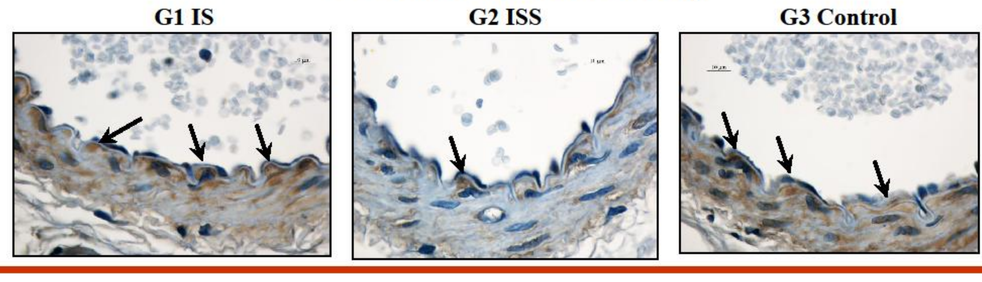
VCAM-1 in Mesenteric Artery



eNOS in Aorta



eNOS in Mesenteric Artery



CONCLUSIONS

- These results suggest that the potential association between i.v. iron administration and vascular wall damage could be more likely linked to a particular ISS rather to IS itself, this due to subtle physical-chemistry differences between some ISS and the originator IS.
- This particular situation may be responsible to produce biological reactions in vascular tissue.

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