

The Possible Role of Medical

Ozone in Angiogenesis



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Introduction

Angiogenesis

- is a progressive multistage and multifactorial vascular remodeling cascade process

[Carmeliat & Collen, 1997].

- is characterized by tight regulation both spatially and temporally

[Cross Claesson- Welsh, 2001 & Oettgen et al., 2001].

Angiogenesis

- **Mainly induces formation of new capillaries from already present ones to improve tissue oxygenation**

[Cao et al., 2001]

- **The capillary density is an important determinant of tissue O₂ supply in the mammalian skeletal muscle**

[Annex et al., 1999].

Material & Methods

To elucidate if medical ozone is able to induce angiogenesis, we used three different doses (75, 40 & 4 $\mu\text{g O}_3$ / ml O_2) in white albino rats by i.p. injection. Angiogenesis was assessed in both skeletal and cardiac muscle at the end of the study using morphometric methods:

➤ *Capillary density* (cap. dens.,) & number of muscle fibers per field were counted, the ratio of cap. dens. / m. fib. (C / F) was calculated.

➤ Perimeter of m. f. s was measured.

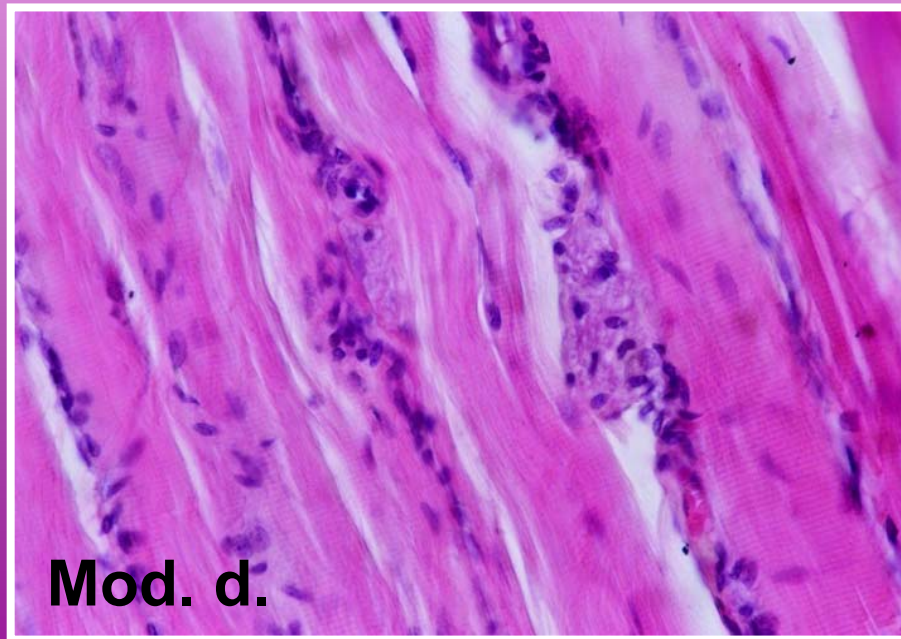
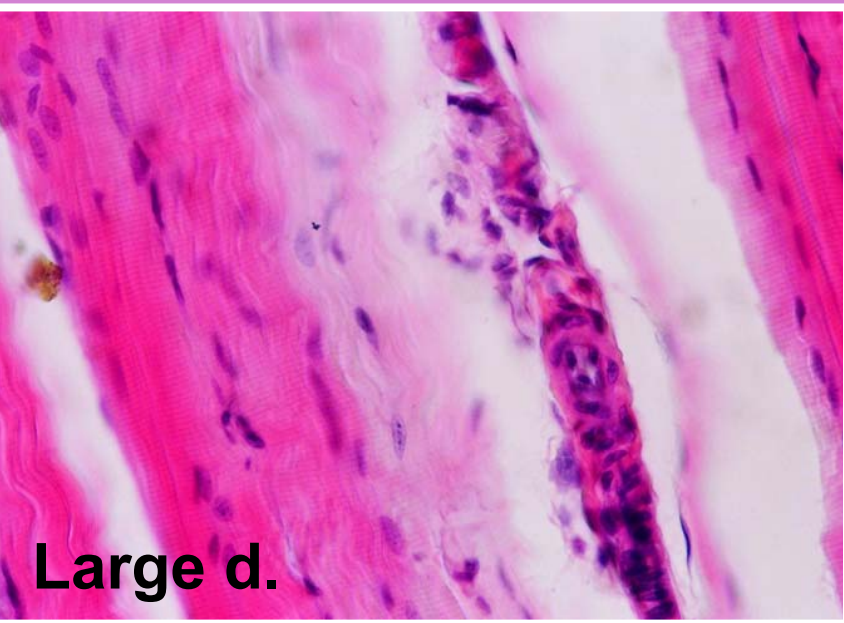
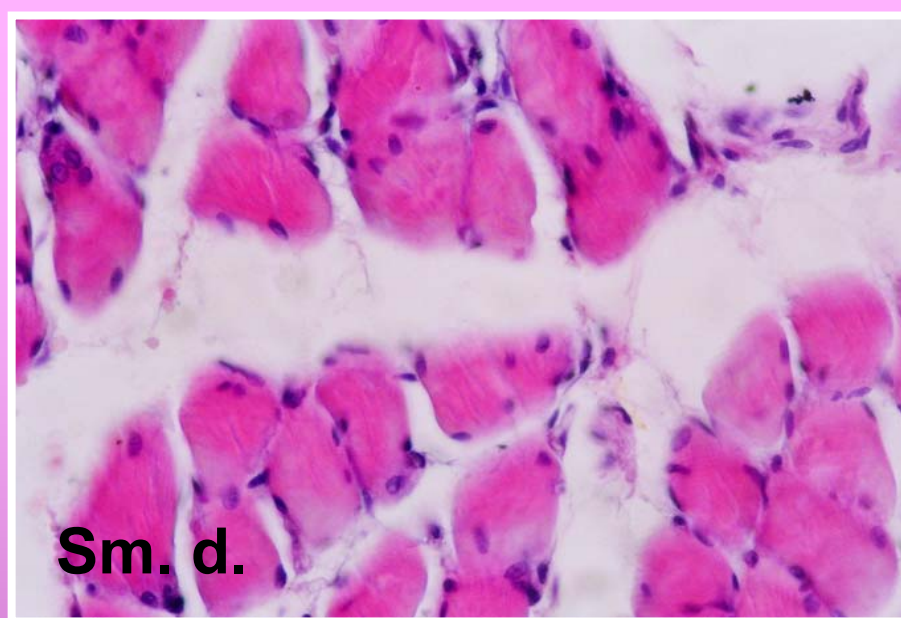
Our data collectively are in favor of:

- Occurrence of endogenous induction of angiogenesis in both cardiac and skeletal muscle by **medical O₃** in the three doses used.
- The “smallest dose with longest duration” group was the most efficient and physiologic.

C/F soleus m.	Control	Small dose	Mod. dose	Large dose
Mean	0.1011	0.2900	0.2771	0.2567
St. Dev.	0.0072	0.0189	0.0170	0.0163
P1	<0.001			
P2		P<0.001	P<0.001	P<0.001

Cap. dens. Soleus m. (no / mm ²)	Control	Small dose	Mod. dose	Large dose
Mean	535.7908	679.4647	660.6840	837.3858
St. Dev.	32.6494	36.1843	34.8657	20.3072
P1	<0.001			
P2		P<0.001	P<0.001	P<0.001

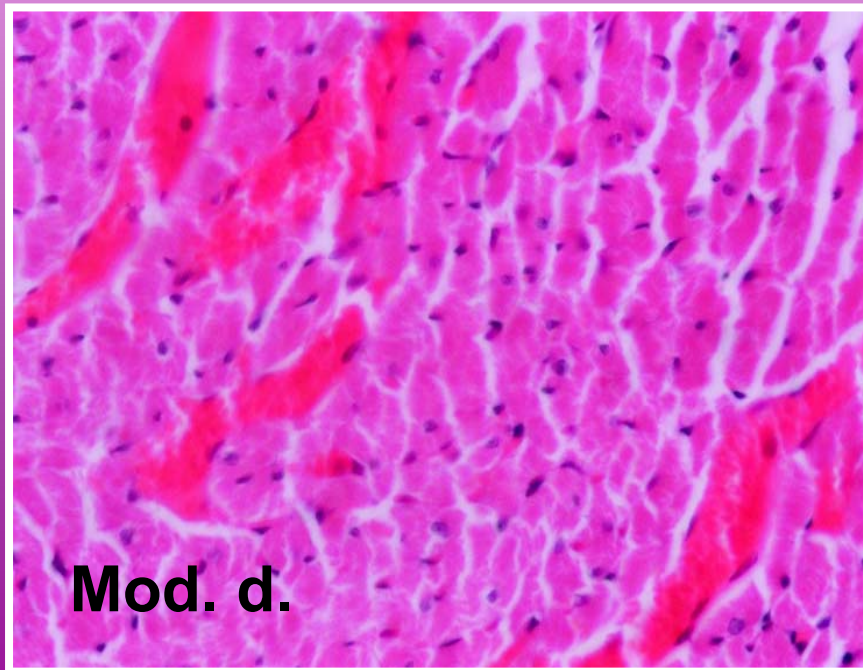
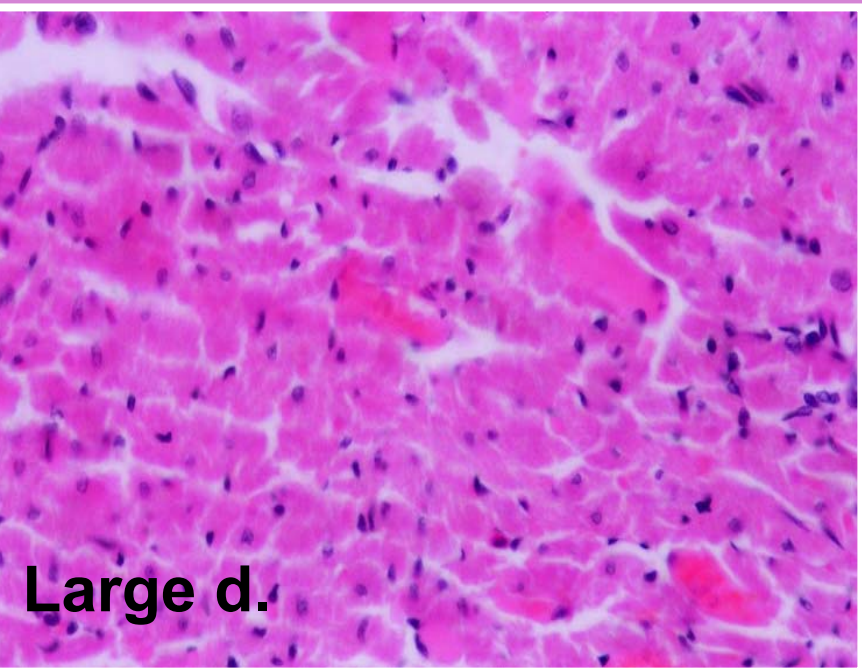
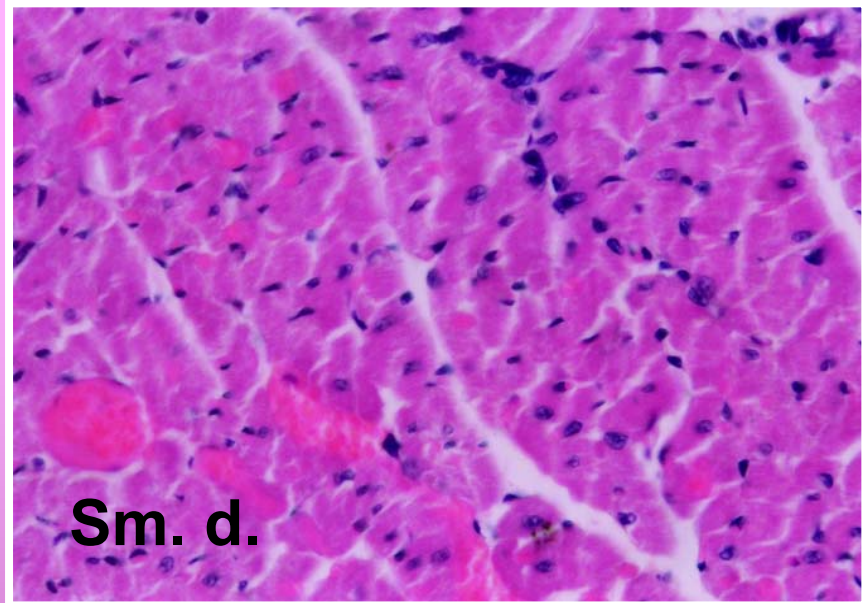
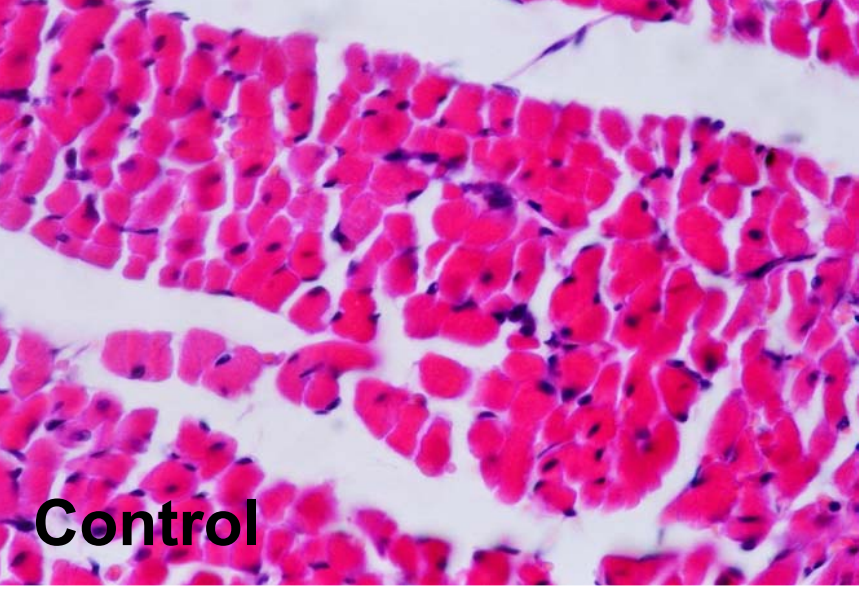
Perimeter soleus m. (μ m)	Control	Small dose	Mod. Dose	Large dose
Mean	118.8450	122.6583	139.4017	105.6833
St. Dev	2.0848	6.6676	17.0286	5.3618
P1	<0.001			
P2		NS	0.001	0.027



C/F cardiac m.	Control	Small dose	Mod. dose	Large dose
Mean	0.0270	0.0504	0.0689	0.0522
St. Dev.	0.0048	0.0117	0.0105	0.0441
P1	< 0.001			
P2		<0.001	<0.001	0.001

Cap. dens. cardiac m. (no / mm ²)	Control	Small dose	Mod. Dose	Large dose
Mean	184.0741	266.6497	383.9159	296.2773
St. Dev.	27.6356	62.4683	52.3630	39.5879
P1	<0.001			
P2		<0.001	<0.001	<0.001

Perimeter cardiac m. (μ m)	Control	Small dose	Mod. Dose	Large dose
Mean	39.9350	48.2320	57.5167	51.0522
St. Dev	4.7540	2.4313	5.6831	4.9769
P1	<0.001			
P2		<0.001	<0.001	<0.001



RBC (millions/mm³)	Control	Small dose	Mod. dose	Large dose
Mean	6.2330	7.0233	6.6013	5.8050
St. Dev.	0.3366	1.4404	0.1501	0.9645
P1	0.047			
P2		0.060	NS	NS

HGB (gm/dl)	Control	Small dose	Mod. dose	Large dose
Mean	12.3200	12.8167	12.1500	10.6625
St. Dev.	0.3225	0.8277	0.2268	1.8118
P1	P < 0.001			
P2		NS	NS	0.001

P1 = is the P value for intergroup comparison.

P2 = is the detailed comparison between control vs other groups.

HCT (%)	Control	Small dose	Mod. dose	Large dose
Mean	38.6500	42.2667	38.0125	35.0500
St. Dev.	1.0255	4.8412	1.0494	3.8619
P1	P < 0.001			
P2		0.016	NS	0.030

MCV (fl)	Control	Small dose	Mod.dose	Large dose
Mean	61.0300	57.9167	57.9750	66.6500
St. Dev.	0.7025	2.4954	1.8053	9.8901
P1	0.002			
P2		NS	NS	0.019

P1 = is the P value for intergroup comparison.

P2 = is the detailed comparison between control vs other groups.

Eosinophils %	Control	Small dose	Mod. dose	Large dose
Mean	1.8000	3.5000	1.7500	1.6250
St. Dev.	0.9189	1.7321	0.2500	0.7440
P1				
P2		0.002	NS	NS

Basophils %	Control	Small dose	Mod. dose	Large dose
Mean	0.5000	0.0000	0.0000	0.000
St. Dev.	0.5774	0.0000	0.000	0.000
P1	<0.001			
P2		< 0.001	< 0.001	< 0.001

BMI (gm/cm²)	Conteol	Small dose	Mod. dose	Large dose
Mean	0.5071	0.6158	0.4818	0.5200
St. Dev	0.0341	0.2714	0.0479	0.0245
P1	NS			
P2		0.040	NS	NS

WBC ($10^3/\text{mm}^3$)	Control	Small dose	Mod. dose	Large dose
Mean	5.6400	6.5583	4.6125	11.5313
St. Dev.	1.2474	1.7594	1.3789	7.3776
P1	0.002			
P2		NS	NS	0.002

Segmental (%)	Control	Small dose	Mod. dose	Large dose
Mean	27.1000	29.3333	24.7500	20.500
St. Dev.	2.1318	11.1952	1.6690	4.2762
P1	0.050			
P2		NS	NS	0.048

P1 = is the P value for intergroup comparison.

P2 = is the detailed comparison between control vs other groups.

Lymphocytes (%)	Control	Small dose	Mod. dose	Large dose
Mean	69.1000	64.5833	73.2500	76.0000
St. Dev.	1.8529	10.2820	1.5811	3.9279
P1	0.002			
P2		NS	NS	0.026

Monocytes (%)	Control	Small dose	Mod. dose	Large dose
Mean	2.400	1.7500	0.3750	1.8750
St. Dev.	0.6992	1.2154	0.2631	0.6409
P1	<0.001			
P2		NS	P<0.001	NS

P1 = is the P value for intergroup comparison.

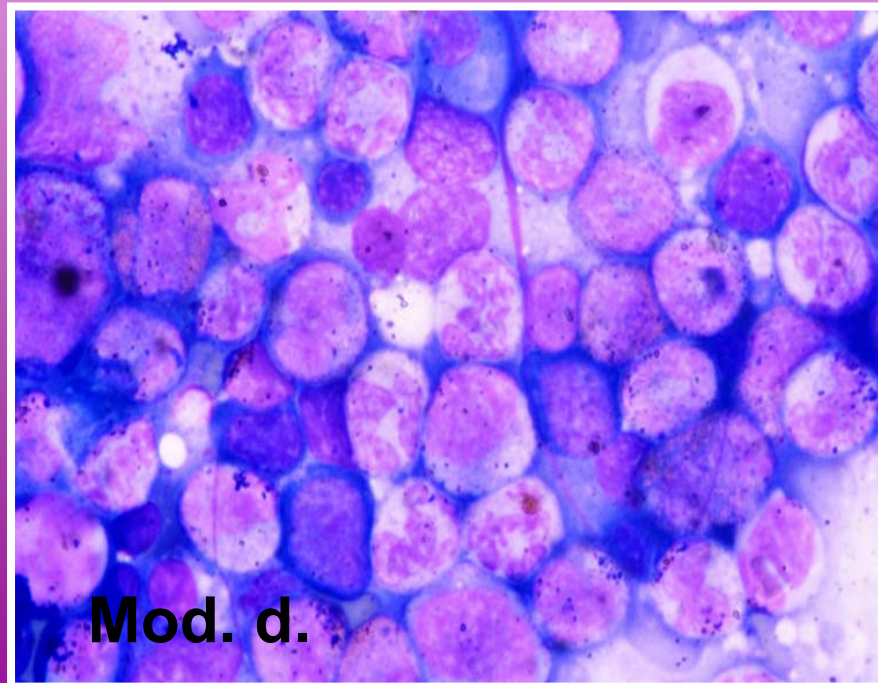
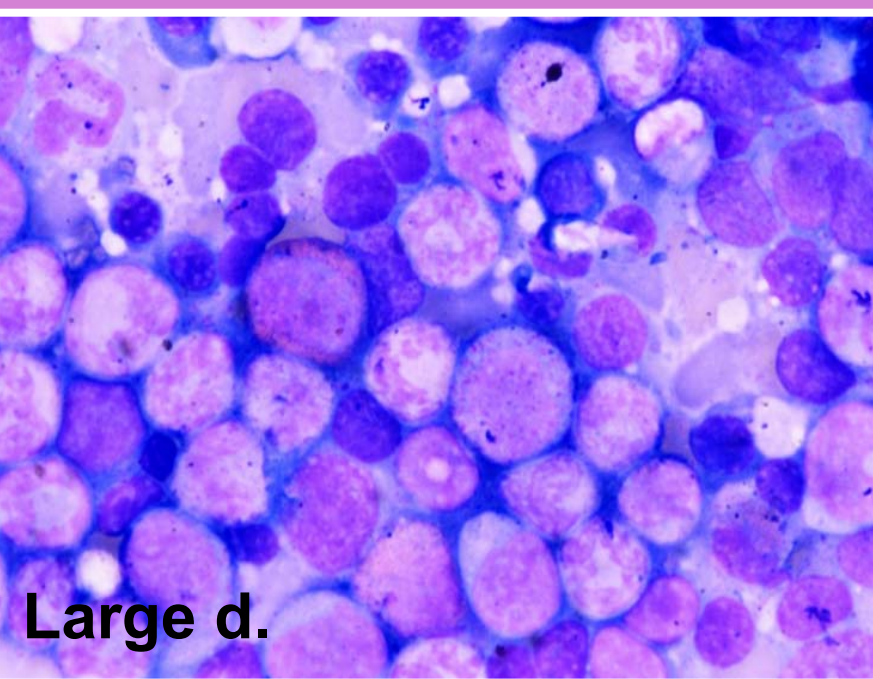
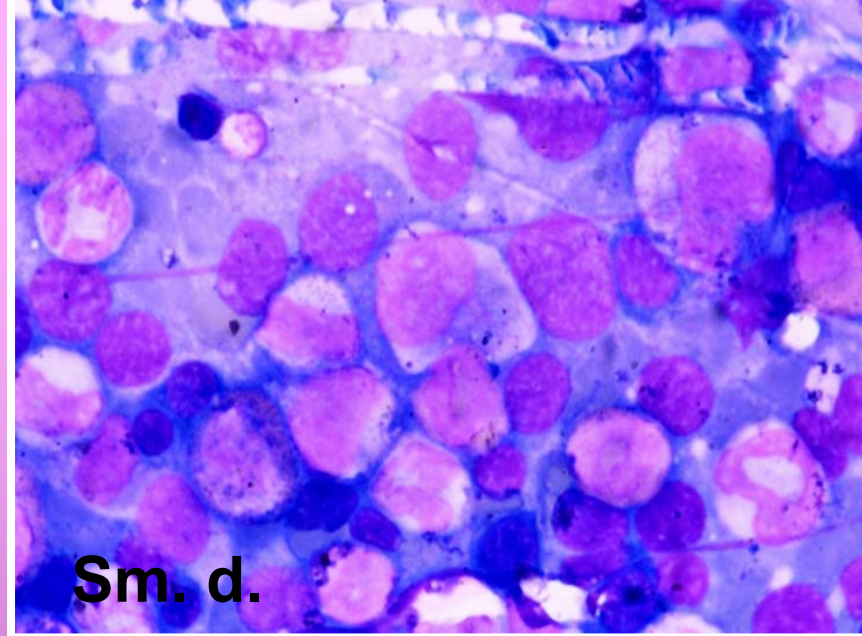
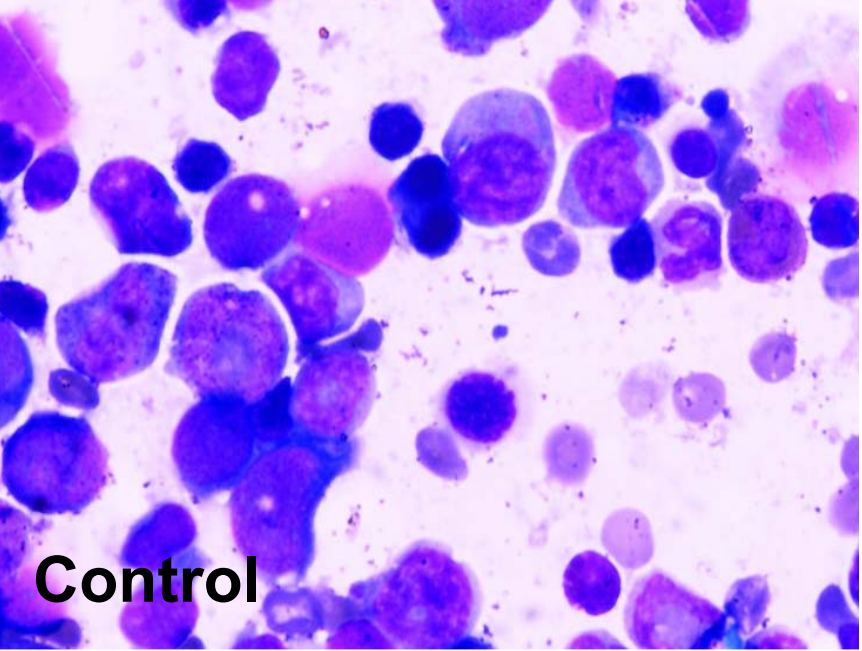
P2 = is the detailed comparison between control vs other groups.

Platelets (10³/mm³)	Control	Small dose	Mod. dose	Large dose
Mean	965.2000	1058.5000	1053.3750	808.5000
St. Dev.	340.2704	158.1728	71.5401	107.1141
P1	0.055			
P2		NS	NS	NS

Fibrinogen (gm/L)	Control	Small dose	Mod. dose	Large dose
Mean	2.3660	2.9767	1.8960	3.5290
St. Dev.	0.3204	0.6394	0.3606	0.6448
P1	<0.001			
P2		0.009	0.051	P<0.001

P1 = is the P value for intergroup comparison.

P2 = is the detailed comparison between control vs other groups.



INF-γ (pg /ml)	Control	Small dose	Mod. dose	Large dose
Mean	108.2938	116.0400	120.8529	216.6857
St. Dev.	16.3355	9.6625	1.9348	93.1394
P1	0.001			
P2		NS	NS	P<0.001

TNF-α (pg/ml)	Control	Small dose	Mod. dose	Large dose
Mean	15.0556	10.3000	20.7286	23.4833
St. Dev.	2.7487	1.0000	7.8496	5.9115
P1	<0.001			
P2		NS	0.032	0.003

P1 = is the P value for intergroup comparison.

P2 = is the detailed comparison between control vs other groups.

MDA ($\mu\text{mol/L}$)	Control	Small dose	Mod. dose	Large dose
Mean	3.1139	5.2044	4.1240	3.7900
St. Dev.	0.06142	0.6188	0.1723	0.2654
P1	<0.001			
P2		P<0.001	P<0.001	P<0.001

LDH (U/L)	Control	Small dose	Mod. dose	Large dose
Mean	297.8250	197.3513	85.8362	1329.3850
St. Dev.	29.1004	85.5123	16.8045	282.7791
P1	<0.001			
P2		0.019	P<0.001	P<0.001

P1 = is the P value for intergroup comparison.

P2 = is the detailed comparison between control vs other groups.

CPK (U/L)	Control	Small dose	Mod. dose	Large dose
Mean	307.4656	165.2800	326.1188	607.4900
St. Dev.	53.0163	45.4661	39.6316	269.1614
P1	<0.001			
P2		0.003	NS	<0.001

Act. (per 5 mins.)	Control	Small dose	Mod. dose	Large dose
Mean	11.6667	17.5556	27.6250	1.5
St. Dev.	4.0620	6.7103	3.5026	0.7071
P1	<0.001			
P2		0.011	<0.001	<0.001

P1 = is the P value for intergroup comparison.

P2 = is the detailed comparison between control vs other groups.

	Capillary density (S.)			Capillary density (C.)	
Small d.	r	(P value)	Small d.	r	(P value)
RBCs	0.904*	(0.013)	C/F (C.)	0.994**	(<0.001)
INF- γ	-1.000**	(<0.001)	Perim. (C.)	-0.631	(0.050)
Moderate d.			Moderate d.		
C/F (C)	-0.894*	(0.016)	C/F (C.)	0.699*	(0.036)
Cap. dens. (C)	-0.851*	(0.032)	Cap. dens. (S)	-0.851*	(0.032)
			Activity	-0.822*	(0.012)
Large d.			Large d.		
LDH	-1.000**	-	C / F (C.)	0.867**	(0.003)
Perim. (S)	0.864*	(0.027)			
Eosin.%	0.903*	(0.014)			
Control			Control		
LDH	0.823*	(0.044)	C/F (C.)	0.841**	(0.002)
CPK	0.971**	(0.001)	TNF- α	-.859**	(0.006)
Basoph. %	1.000**	-			

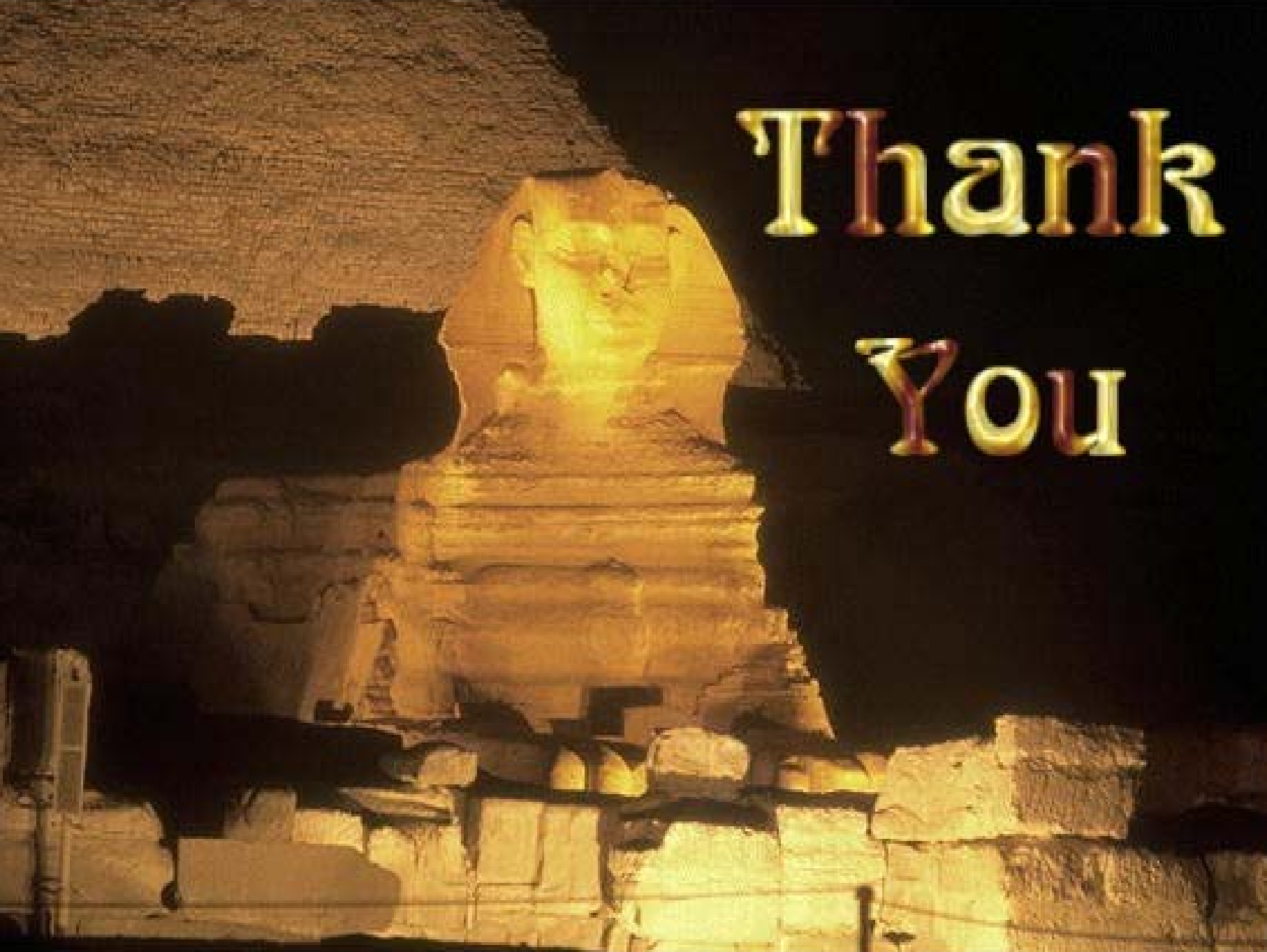
Conclusion & Recommendation

- Repeated medical ozone administration in small dose can be encouraged as a “physiological therapeutic endogenous angiogenic procedure” enhancing all the steps of the multifactorial angiogenic cascade.

Conclusion & Recommendation

Cont.

From this aspect, medical ozone can be superior to the use of several angiogenic factors, which are liable to interfere with specific constitutional vascular endothelial growth factor (VEGF) isoforms function and can disturb the special pattern of distribution of its receptors.

The Great Sphinx of Giza is the central focus of the image, shown at night. It is illuminated from below, casting a warm, golden glow on its face and the surrounding stone blocks. The background is dark, making the illuminated monument stand out prominently. The text 'Thank You' is overlaid on the right side of the image in a stylized, multi-colored font.

Thank

You