



Remote ischemic conditioning results in oxidative stress reduction and nitrate-nitrite-nitric oxide pathway activation in acute myocardial infarction patients

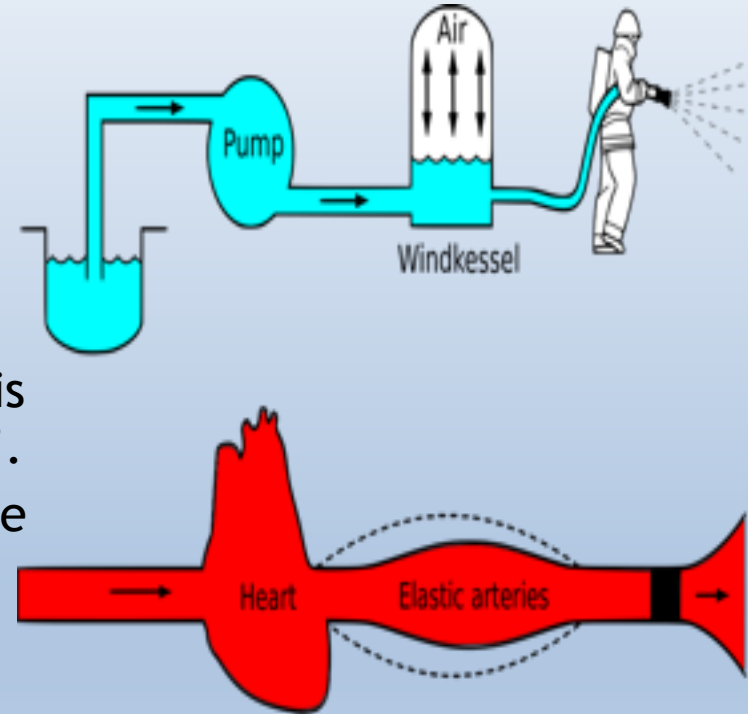
D. Vlastos, I. Ikonomidis, I. Andreadou, P. Efentakis, M. Varoudi, G. Pavlidis, G. Makavos, S. Vlachos, D. Mpenas, H. Triantafyllidi, E. Seitanidi, EK. Iliodromitis, J. Lekakis - University of Athens Medical School, Attikon Hospital, 2nd Department of Cardiology, Athens, Greece

BACKGROUND

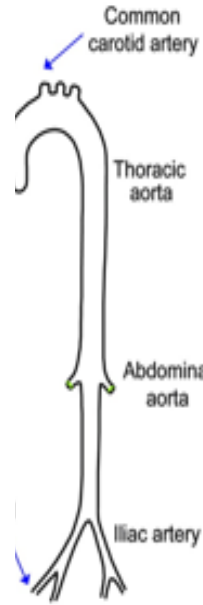
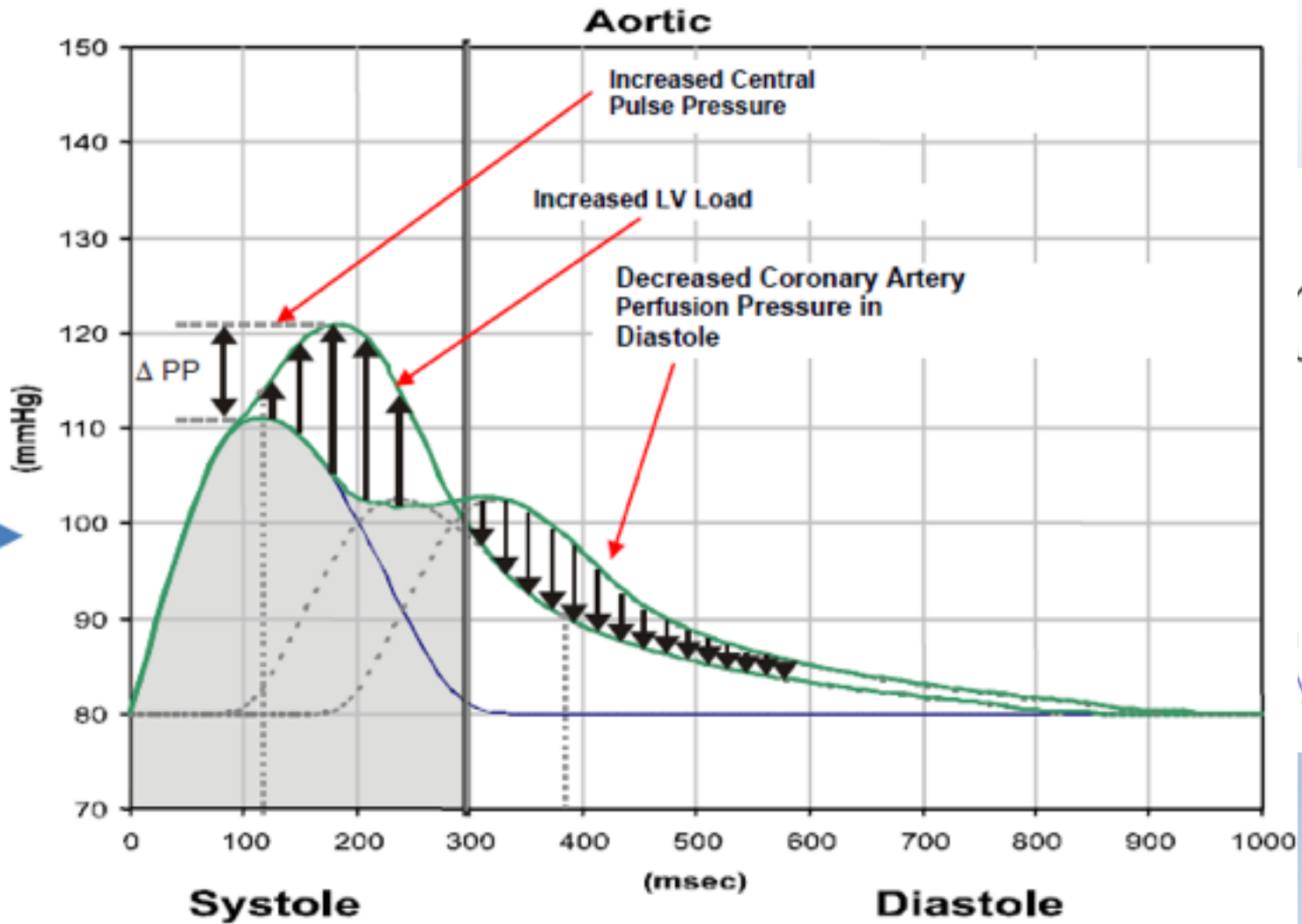
- Remote ischemic conditioning attenuates ischemia-reperfusion injury in patients with STEMI.
- However, its effects on vascular function and biochemical mechanisms are not fully defined.

PULSATILE HEMODYNAMICS

- **Aortic elasticity** plays a major role in the regulation of **blood pressure** and **peripheral blood flow**.
- It allows the damping of the rhythmic left ventricular output and the translation of the pulsatile cardiac pump function into a nearly continuous peripheral blood flow, an effect that is well known as the aortic “ **Windkessel function**”.
- This systolic-diastolic interplay can also affect the heart, **reducing the left ventricular afterload** and **improving the coronary blood flow** and ventricular relaxation.



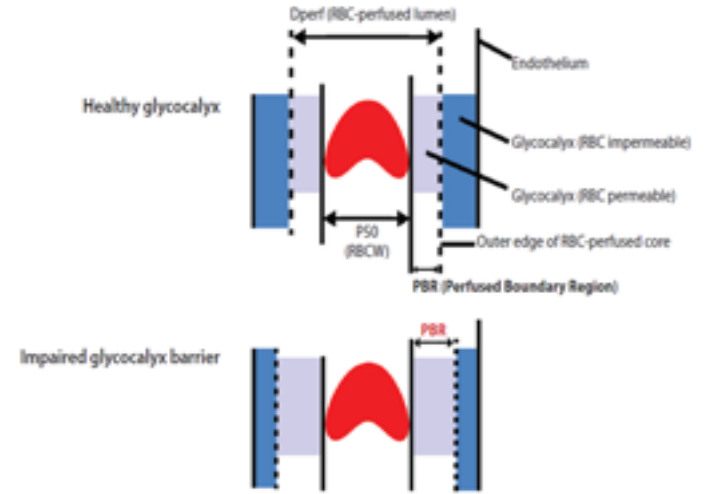
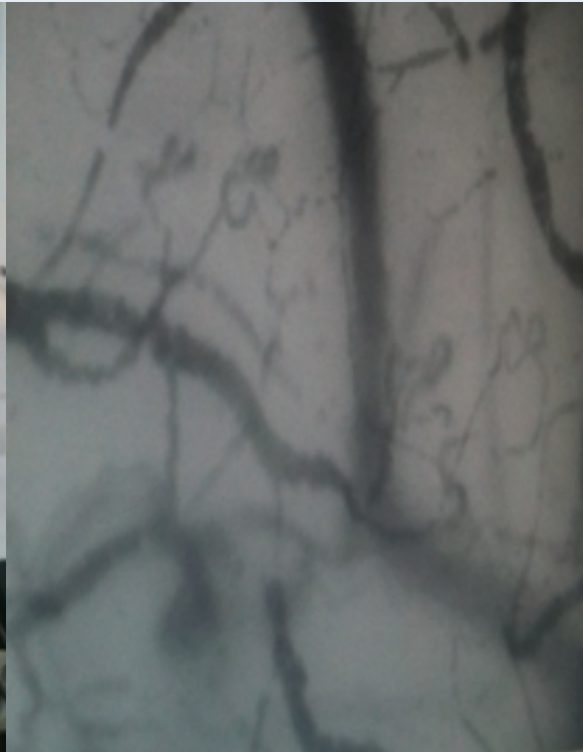
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GLYCOCALYX INTEGRITY

- Endothelial glycocalyx plays a vital role in vascular permeability and inflammation.
- Endothelial glycocalyx damage is associated with lipoprotein influx, macromolecule leakage, adhesion of circulating cells to the endothelium, and imbalance in enzymatic systems such as coagulation and antioxidant defence, as well as an impaired NO release.
- Increased PBR is an accurate index of impaired glycocalyx integrity, and consequently of endothelial dysfunction.

GLYCOCALYX INTEGRITY

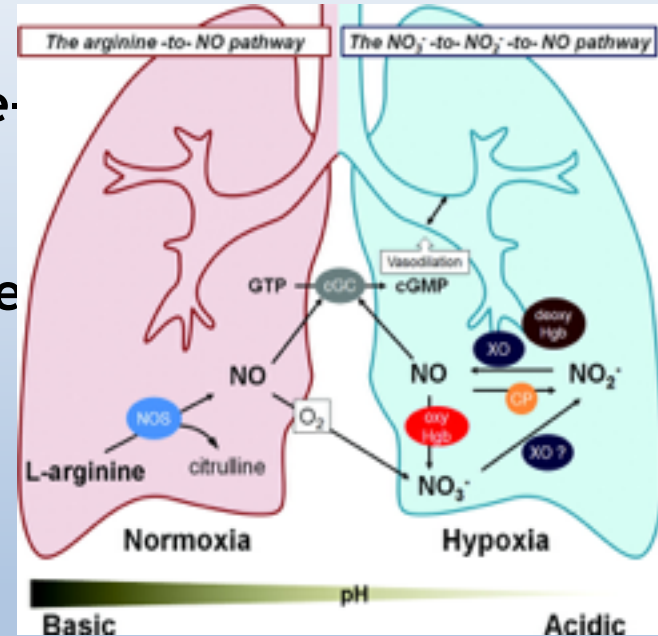


SERUM MDA LEVELS

- Excessive reactive oxygen species (ROS) production plays a significant role in the reperfusion injury mechanism.
- The abruptly reintroduced molecular oxygen into ischemic myocardium undergoes sequential reduction, which leads to oxygen free radicals formation.
- These free radicals react with polyunsaturated fatty acids, forming lipid peroxides and hydroperoxides that cause damage to the sarcolemma and membrane-bound enzymes impairment.
- MDA is one of the products of the aforementioned lipid peroxidation, serving as a reliable index of free-radical induced injury.

NITRATE-NITRITE-NO PATHWAY

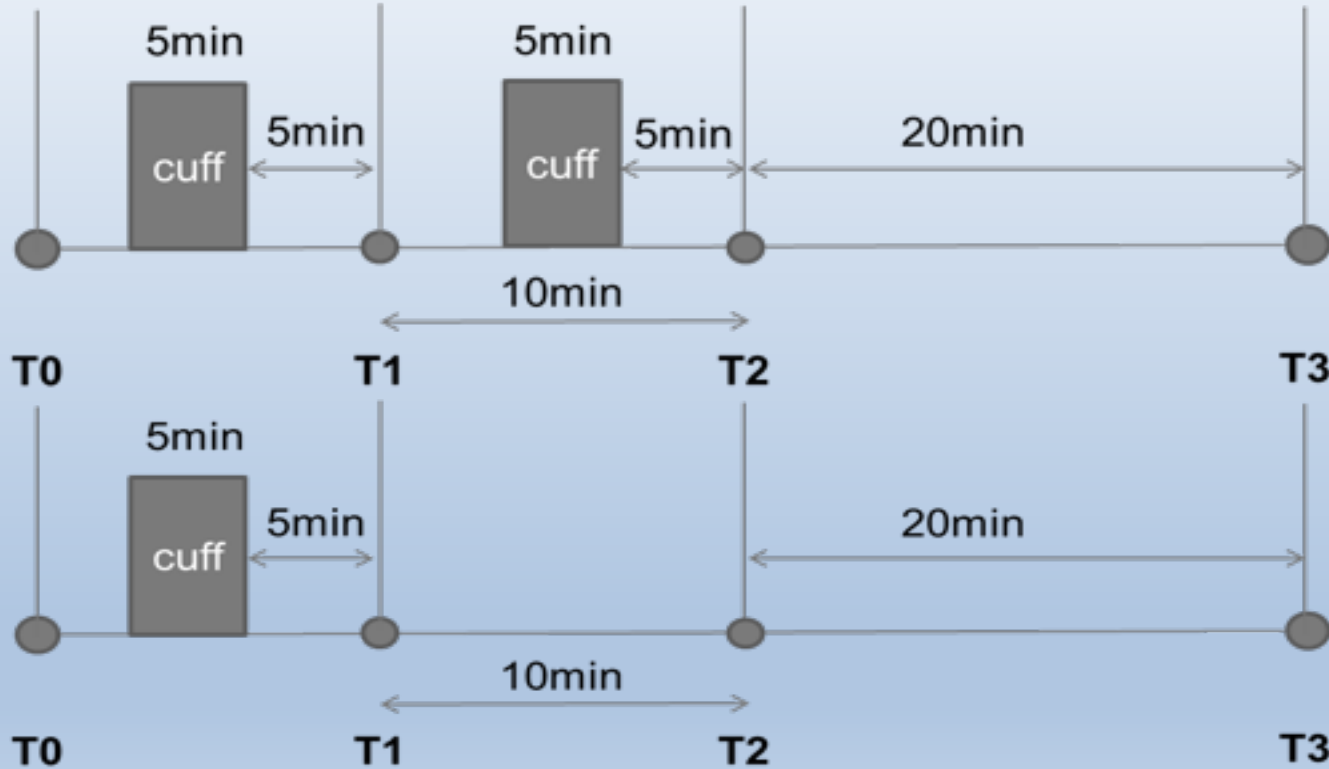
- It has been shown *in vivo* that nitrate and nitrite anions serve as an independent of the L-arginine-NO-synthase source of NO, particularly in the setting of hypoxia.
- Nitrite promotes vasodilation and blood pressure reduction, while by way of mitochondrial electron transfer modulation it attenuates ischemia-reperfusion injury.
- Nitrate is converted to nitrite in the oral cavity by nitrate reductase containing bacteria, and therefore causes similar effects.



METHODS

- We examined **110 patients with STEMI** and **30 healthy controls**.
- Patients were **randomised in 2 remote ischemic conditioning protocols** after a baseline assessment of vascular function (T0):
 - a) one with **two ischemic conditioning stimuli** by brachial cuff inflation of both arms at 200mmHg for 5 min, separated by 15min, and each cuff deflation followed by vascular assessment (T1,T2), and a final vascular assessment (T3) 25 min after 2nd cuff deflation (double cuff inflation: n=55) or
 - b) a second with **omission of the second cuff inflation** (single cuff inflation: n=55).

METHODS



METHODS

In both protocols we measured:

- a) the carotid-femoral pulse wave velocity (**PWV**);
- b) the perfusion boundary region (**PBR-micrometers**) of the sublingual arterial microvessels as a marker of endothelial glycocalyx thickness;
- c) plasma malondialdehyde (**MDA**), **NOx**, and **IL-6** levels as biomarkers of oxidative stress and inflammation.

RESULTS

Patient characteristics	
<i>Age</i>	53±16
<i>Sex</i>	M:80%
<i>BMI</i>	27±4
<i>Hypertension</i>	27% (n=29)
<i>Diabetes mellitus</i>	17% (n=18)
<i>Dyslipidemia</i>	24% (n=26)
<i>Smoking</i>	53% (n=58)
<i>CAD family history</i>	12% (n=13)

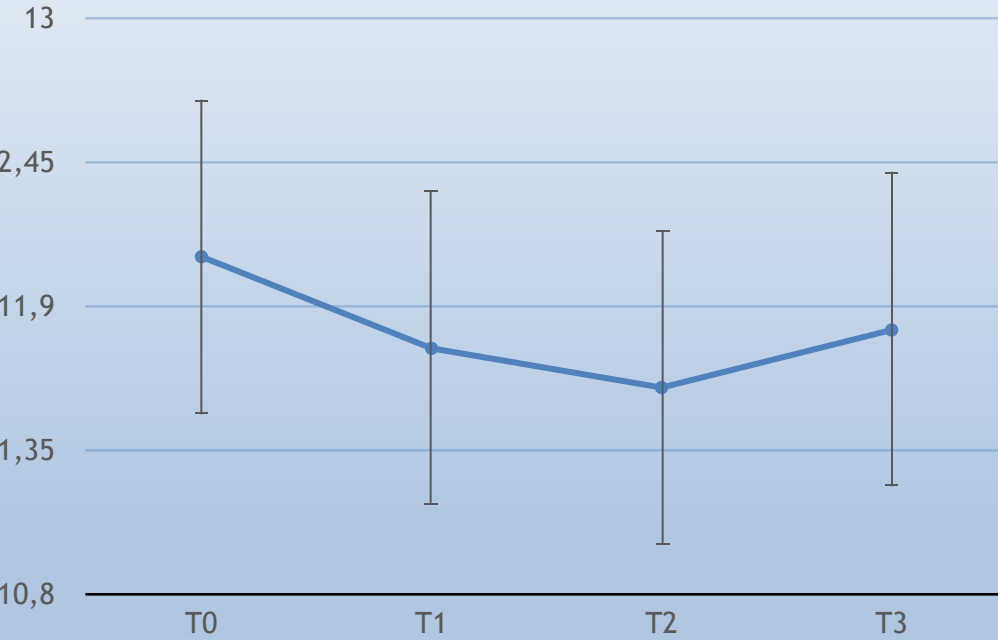
AMI characteristics	
<i>1 vessel disease</i>	42% (n=46)
<i>2 vessel disease</i>	46% (n=51)
<i>3 vessel disease</i>	12% (n=13)
<i>Anterior</i>	47% (n=51)
<i>hs-Troponin</i>	3843 [991-9338] ng/L
<i>CPK</i>	1210 [461-2923] U/L
<i>WBC</i>	8.790±2.577/mcL
<i>CRP</i>	191±3 mg/L

RESULTS

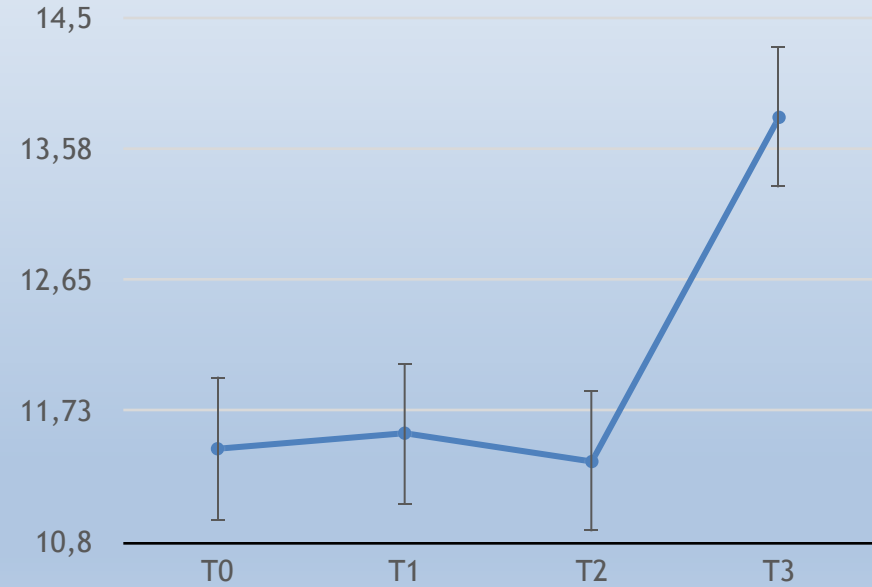
- Compared to the double cuff inflation, the single cuff inflation protocol resulted in a more uniform **aortic elasticity** improvement (PWV T0: **12.09** m/s, T1: **11.74**m/s, T2: **11.59**m/s, T3: **11.81**m/s), with the greatest difference measured at the last vascular assessment (T3: PWV= **11.8** single cuff vs **13.8** m/s double cuff inflation , $p < 0.05$).
- A greater **glycocalyx integrity** restoration was observed in patients with baseline PBR > 2.1 (n=50) in both protocols (mean difference in PBR improvement=0.5 at T1, $p < 0.001$).

RESULTS

PWV-single cuff



PWV-double cuff

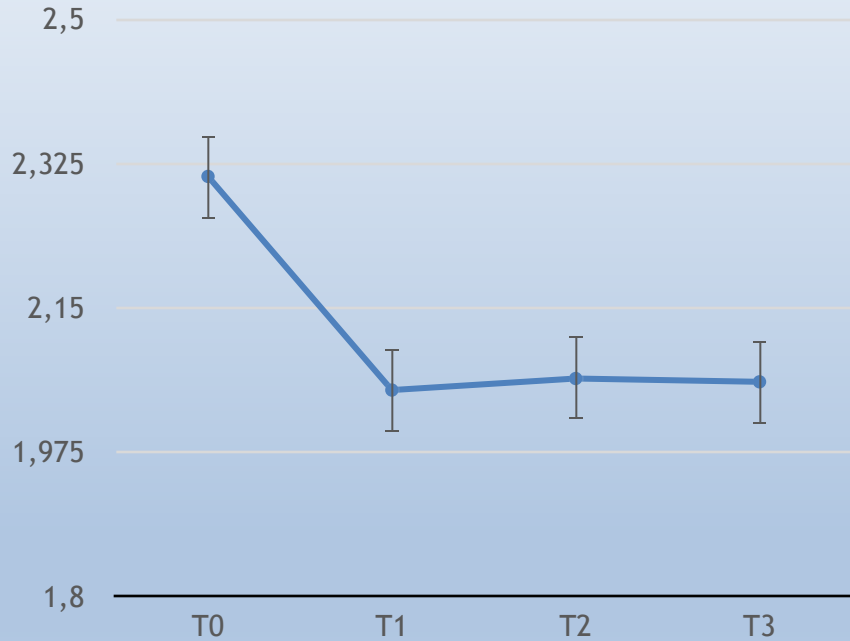


RESULTS

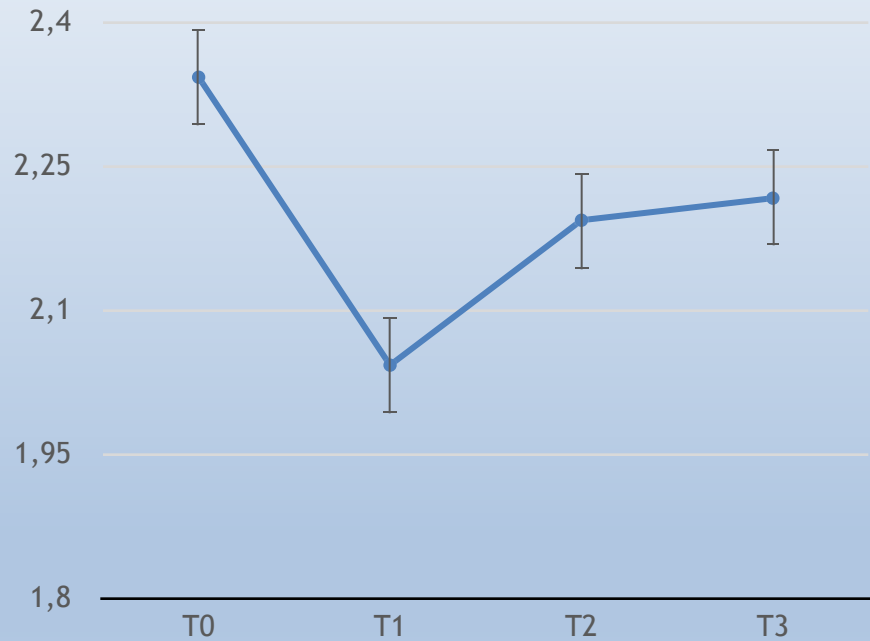
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PBR 5-25 - single cuff



PBR 5-25 - double cuff

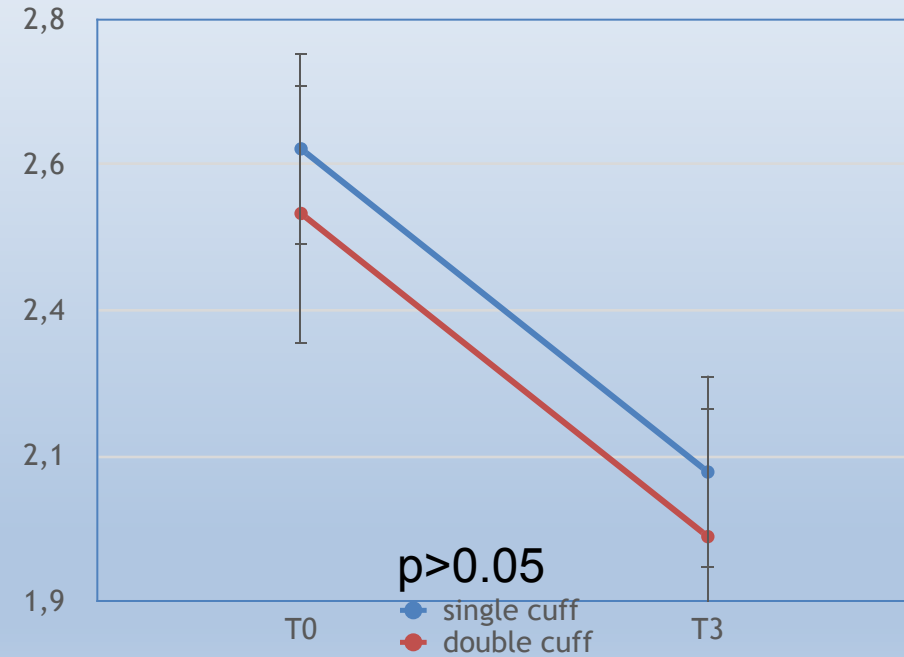


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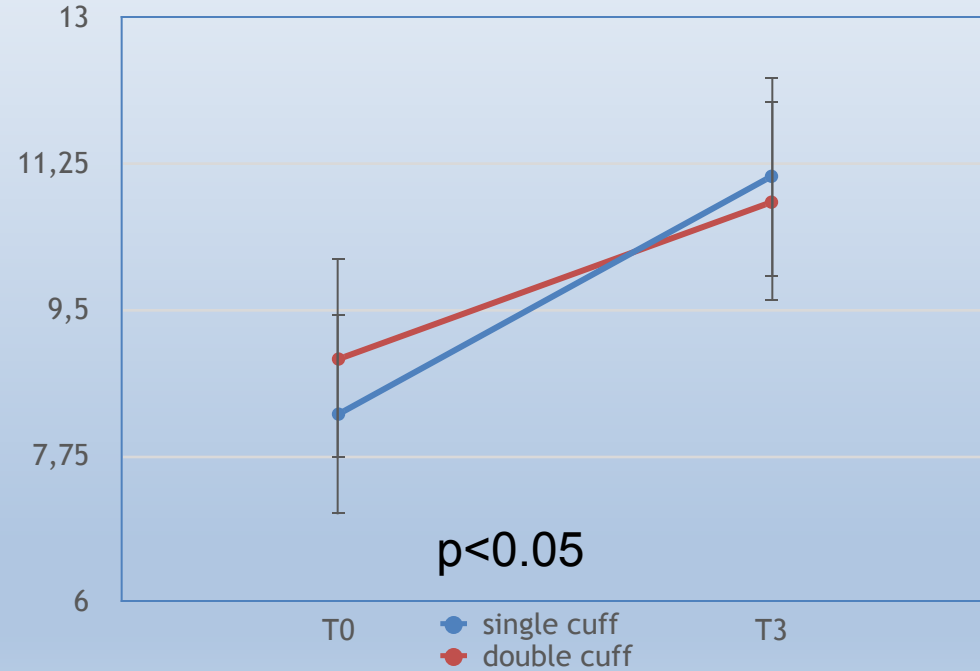
- **MDA was significantly reduced at T3 compared to baseline in STEMI (2.1 ± 0.15 at T3 vs 2.59 ± 0.15 at T0, $p < 0.001$) in both protocols while it remained unchanged in healthy controls.**
- **The single cuff inflation protocol promoted a greater increase in NOx levels compared to the double inflation protocol (T0: 8.25 ± 1.18 to T3: 11.1 ± 2 μM vs T0: 8.91 ± 2 to T3: 10.79 ± 1.18 μM , $p < 0.05$).**
- **IL-6 levels were not affected by our conditioning protocols.**

RESULTS

MDA



NOx

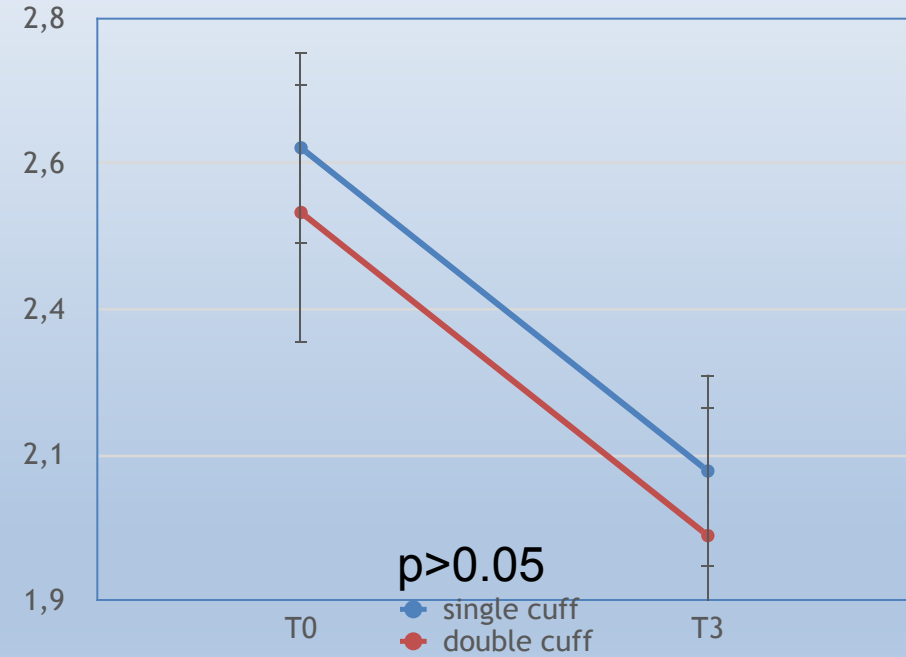


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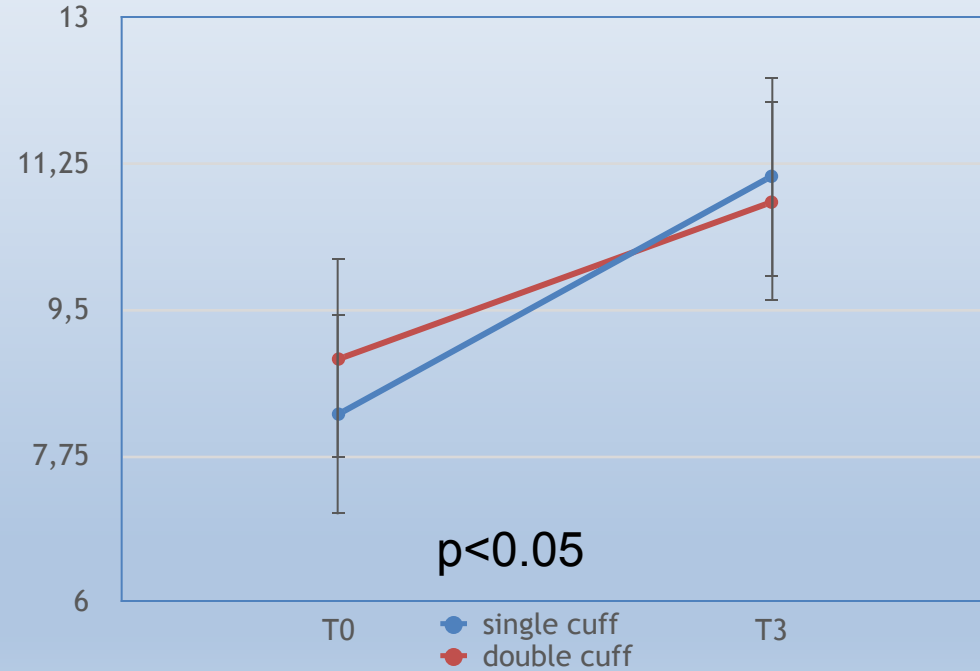
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RESULTS

MDA



NOx



CONCLUSION

- Remote ischemic conditioning by a **single 5-min cuff inflation confers acute short-term improvement of vascular function**, likely through **oxidative stress reduction and nitrate-nitrite-NO pathway activation**.