Sodium Nitrite for Out-of-Hospital Cardiac Arrest

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Disclosures

EMS Medicine Fellowship Director, University of Washington

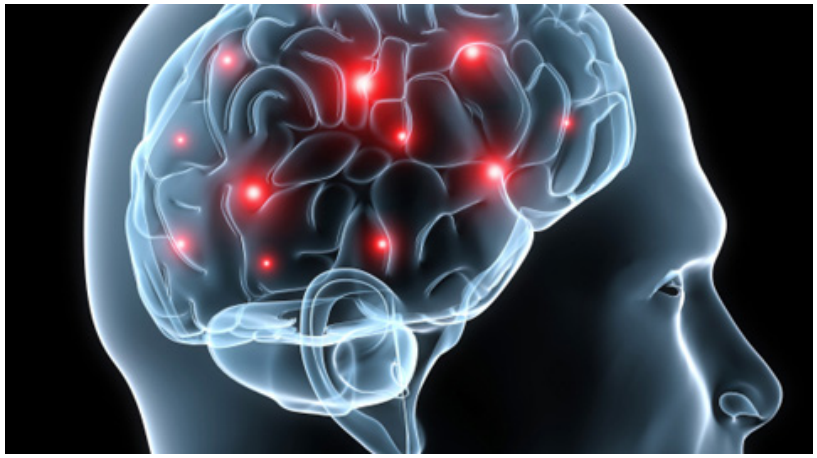
Physio-Control provides a significant grant to partially fund the fellow's salary and benefits.

- I receive travel reimbursement from the fund.

We will discuss a potential indication, not approved by FDA, for an approved drug.

Half of OHCA patients admitted to hospital following restoration of pulses die of brain injury.

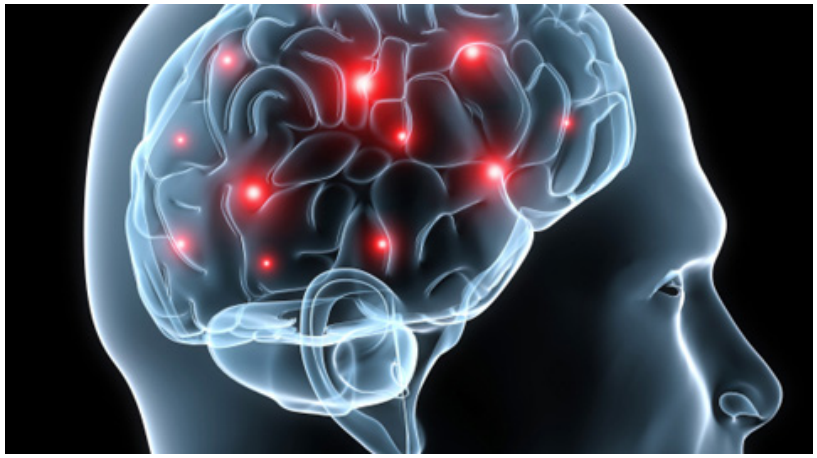
The Hot Dog Study



Time

Electrical

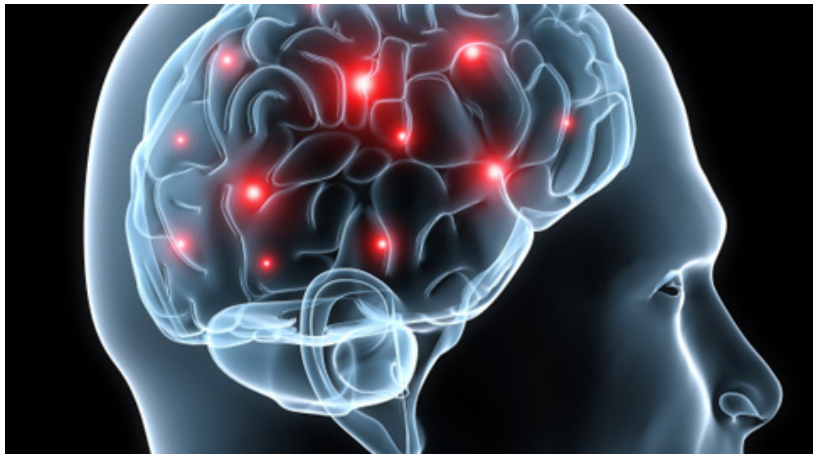
Defibrillation



Time

Hemodynamic

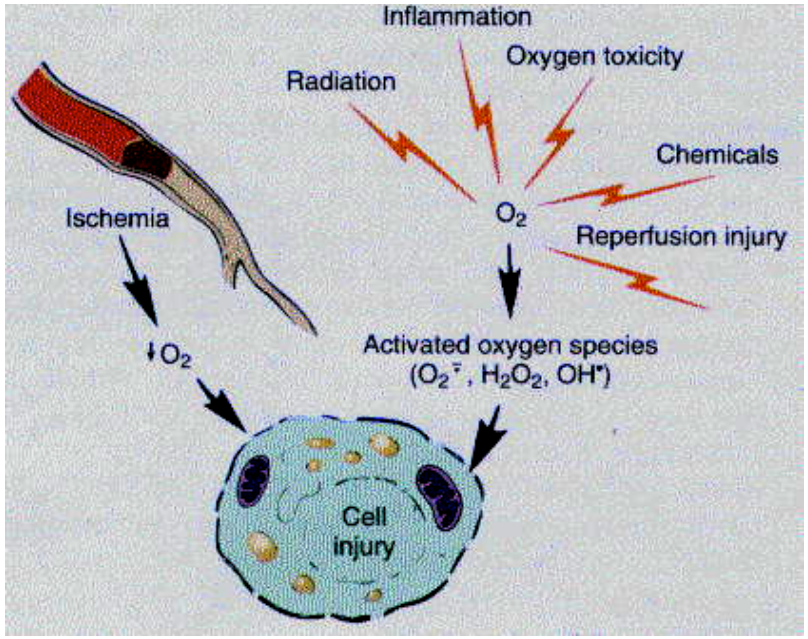
CPR + ? Epinephrine



Time

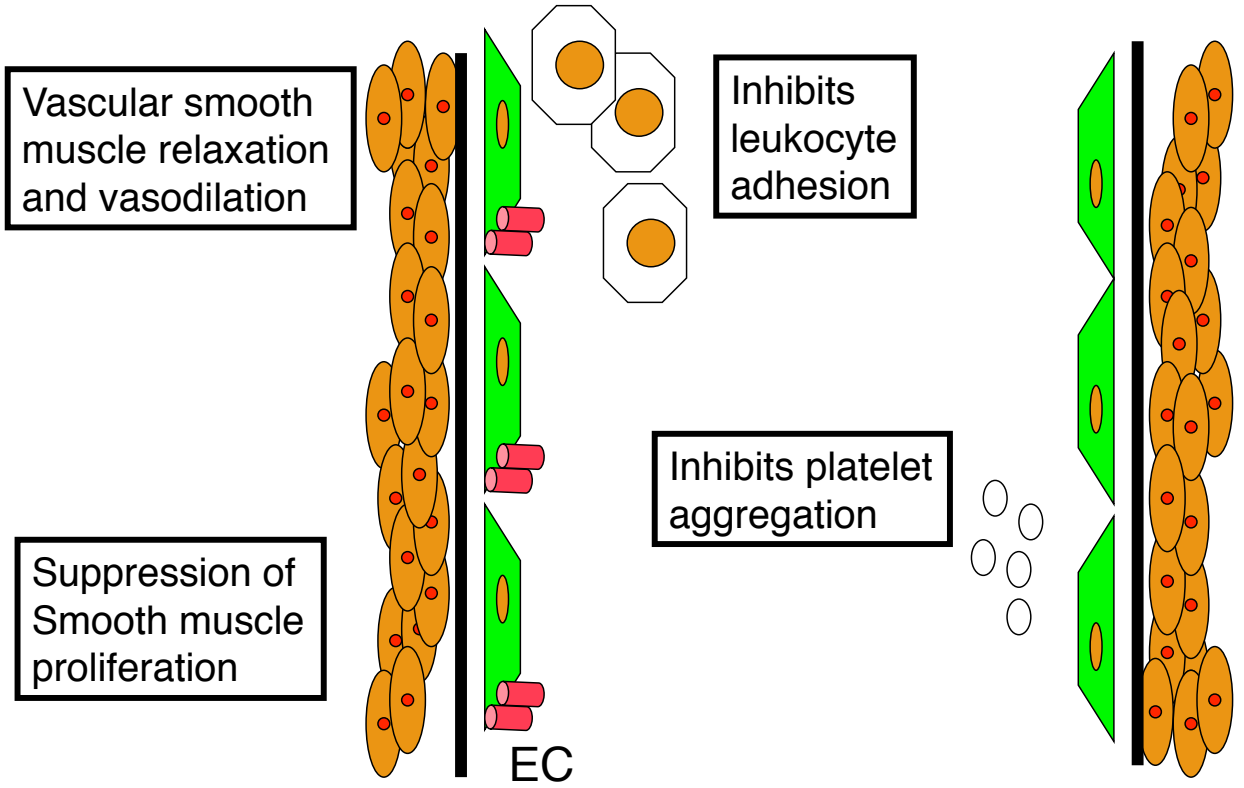
Metabolic

?



It’s all about the mitochrondia.

Known protective effects of nitric oxide



Question

Will increasing nitric oxide (NO) levels in brain tissue improve neurologic outcome following resuscitation from cardiac arrest?

Possible approaches

Inhaled nitric oxide gas

Drugs that directly increase nitric oxide

- Nitroglycerin, Sodium nitroprusside

Drugs that indirectly increase nitric oxide's effect

- Sildenafil

Resuscitation 110 (2017) 6–11

Contents lists available at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Experimental paper

Sodium nitroprusside enhanced cardiopulmonary resuscitation improves short term survival in a porcine model of ischemic refractory ventricular fibrillation☆,☆☆

Demetris Yannopoulos[a,*], Jason A. Bartos[a], Stephen A. George[a], George Sideris[b], Sebastian Voicu[b], Brett Oestreich[a], Timothy Matsuura[c], Kadambari Shekar[c], Jennifer Rees[a], Tom P. Aufderheide[d]

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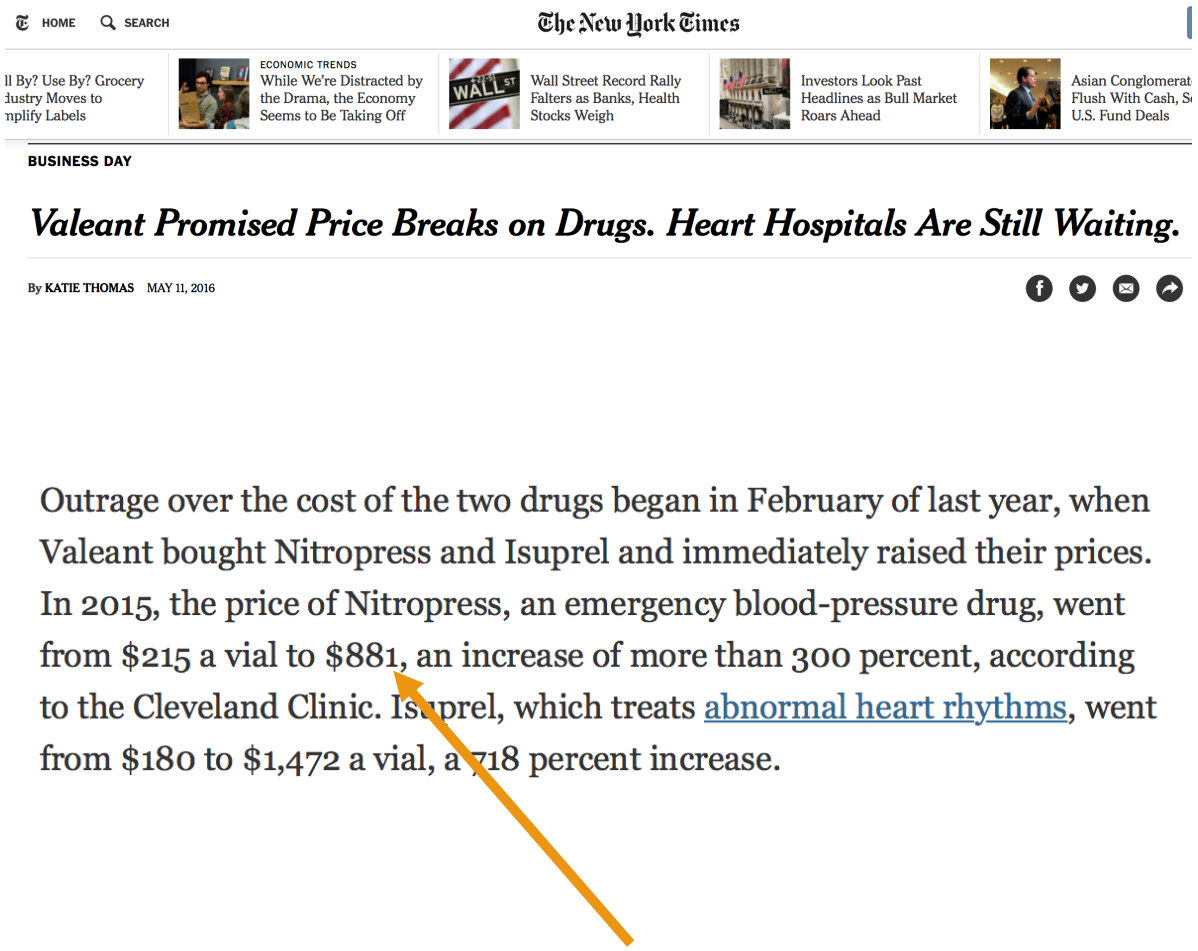
[b] Department of Cardiology, Inserm U942, Lariboisiere Hospital, AP-HP, Paris Diderot University, Paris, France
[c] Department of Integrated Biology & Physiology, University of Minnesota, Minneapolis, MN, United States
[d] Department of Emergency Medicine, Medical College of Wisconsin, Milwaukee, WI, United States

Sodium nitroprusside is not affordable



HOME SEARCH

The New York Times

ll By? Use By? Grocery dustry Moves to nplify Labels

ECONOMIC TRENDS
While We're Distracted by the Drama, the Economy Seems to Be Taking Off

Wall Street Record Rally Falters as Banks, Health Stocks Weigh

Investors Look Past Headlines as Bull Market Roars Ahead

Asian Conglomerat Flush With Cash, S U.S. Fund Deals

BUSINESS DAY

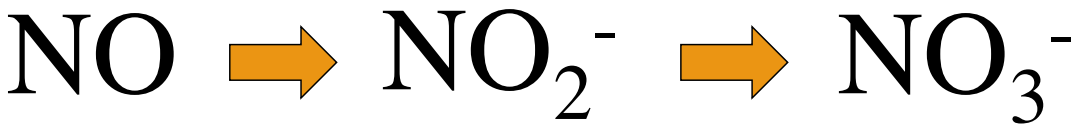
Valeant Promised Price Breaks on Drugs. Heart Hospitals Are Still Waiting.

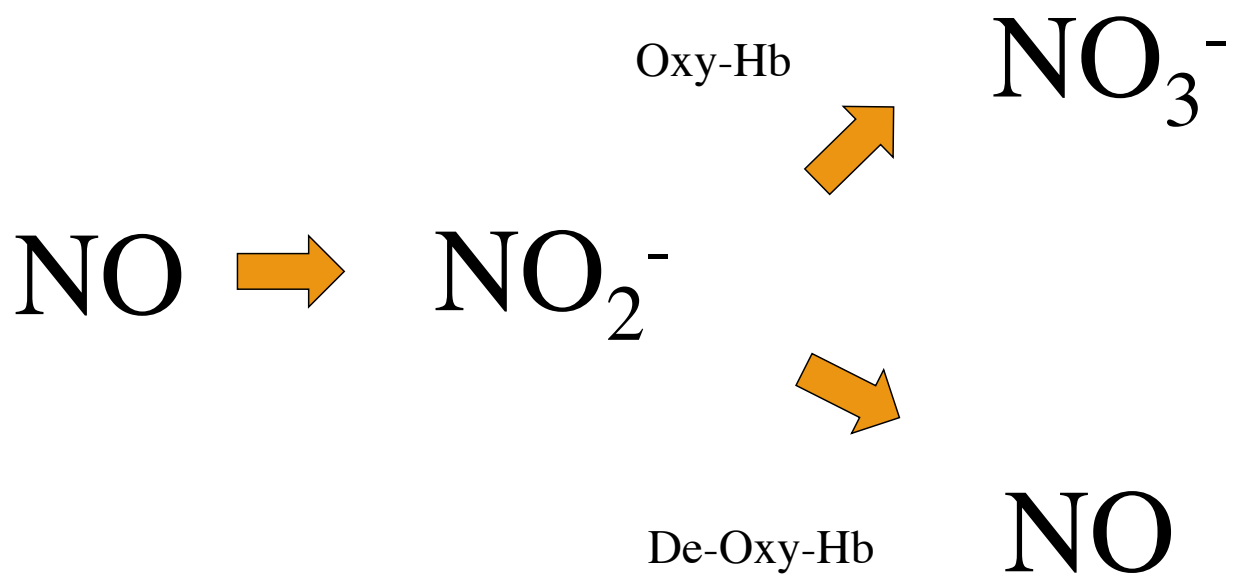
By KATIE THOMAS MAY 11, 2016

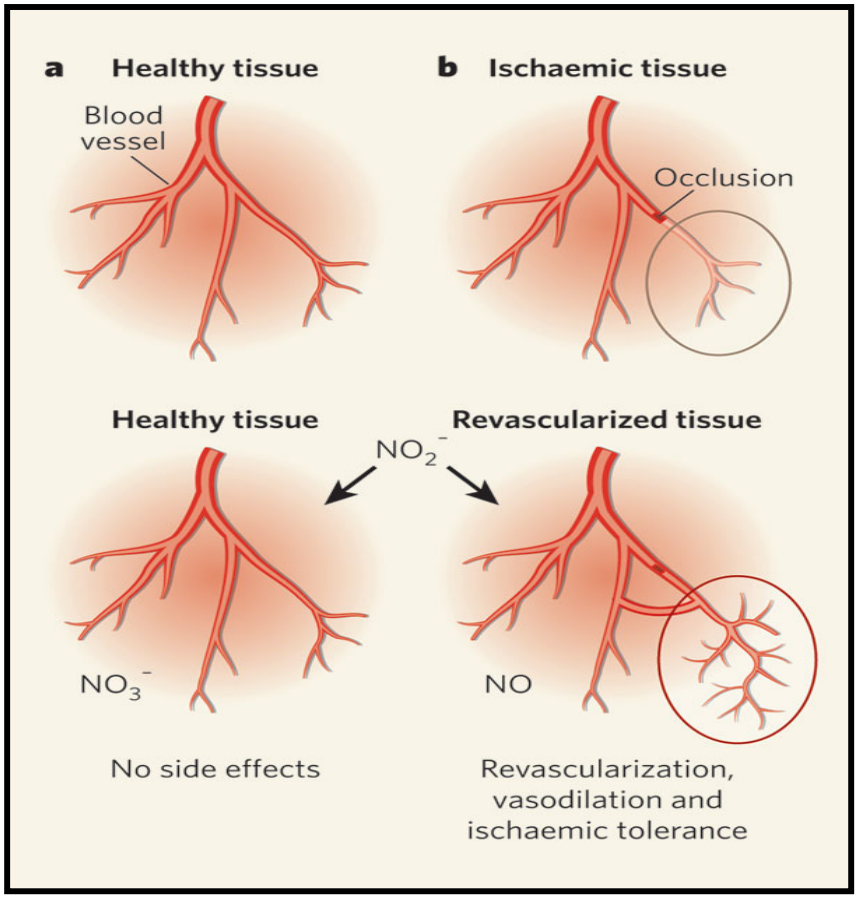
Outrage over the cost of the two drugs began in February of last year, when Valeant bought Nitropress and Isuprel and immediately raised their prices. In 2015, the price of Nitropress, an emergency blood-pressure drug, went from $215 a vial to $881, an increase of more than 300 percent, according to the Cleveland Clinic. Isuprel, which treats abnormal heart rhythms, went from $180 to $1,472 a vial, a 718 percent increase.

Can a different FDA approved drug serve as a source for nitric oxide?

Nitrite Nitrate




Oxy-Hb
NO_3^-
NO
NO_2^-
De-Oxy-Hb
NO

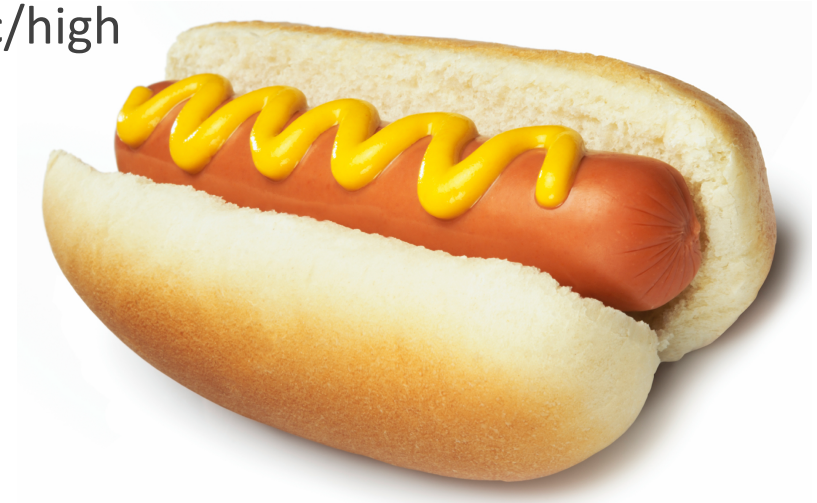

a
Healthy tissue
Blood vessel
b
Ischaemic tissue
Occlusion
Healthy tissue
Revascularized tissue
NO_2^-
NO_3^-
NO
No side effects
Revascularization, vasodilation and ischaemic tolerance

The bad

Nitrite functions as a food preservative.

FDA regulates it.

- Nitrosamines produced during acidic/high heat



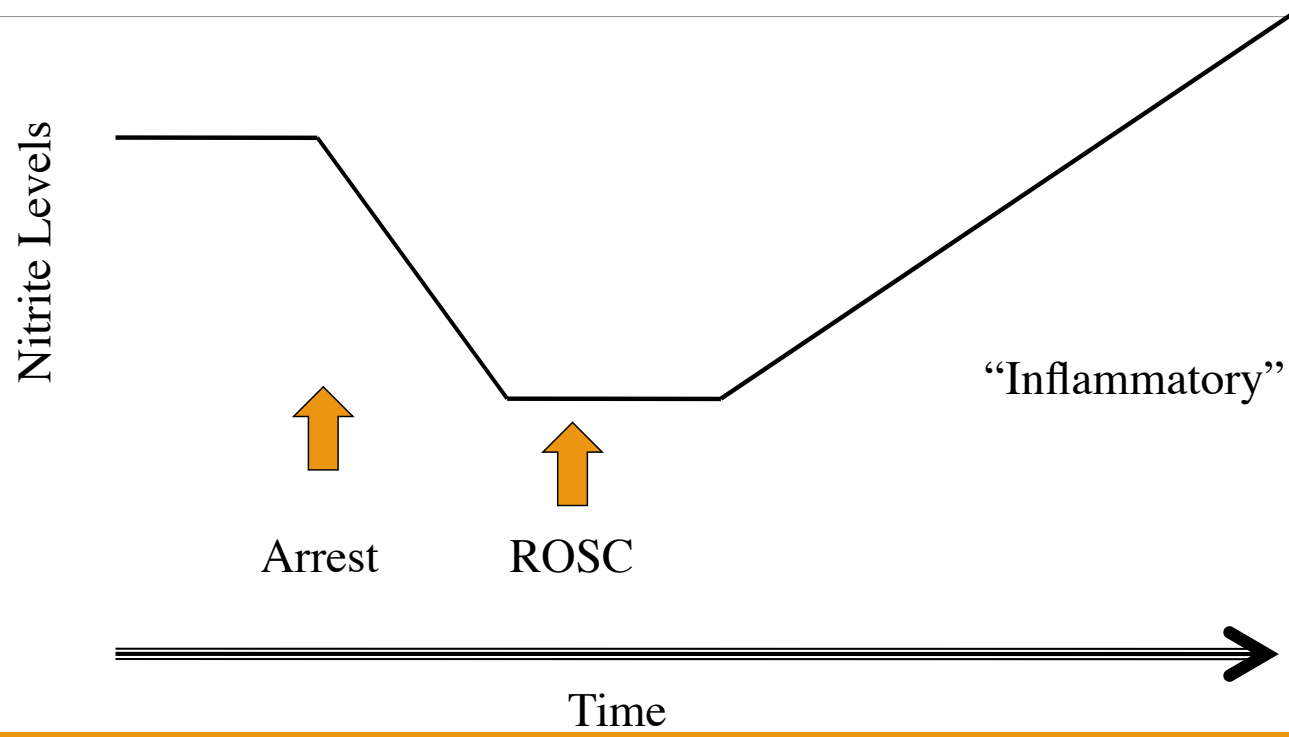
Beet Juice: 22-50 mg nitrite

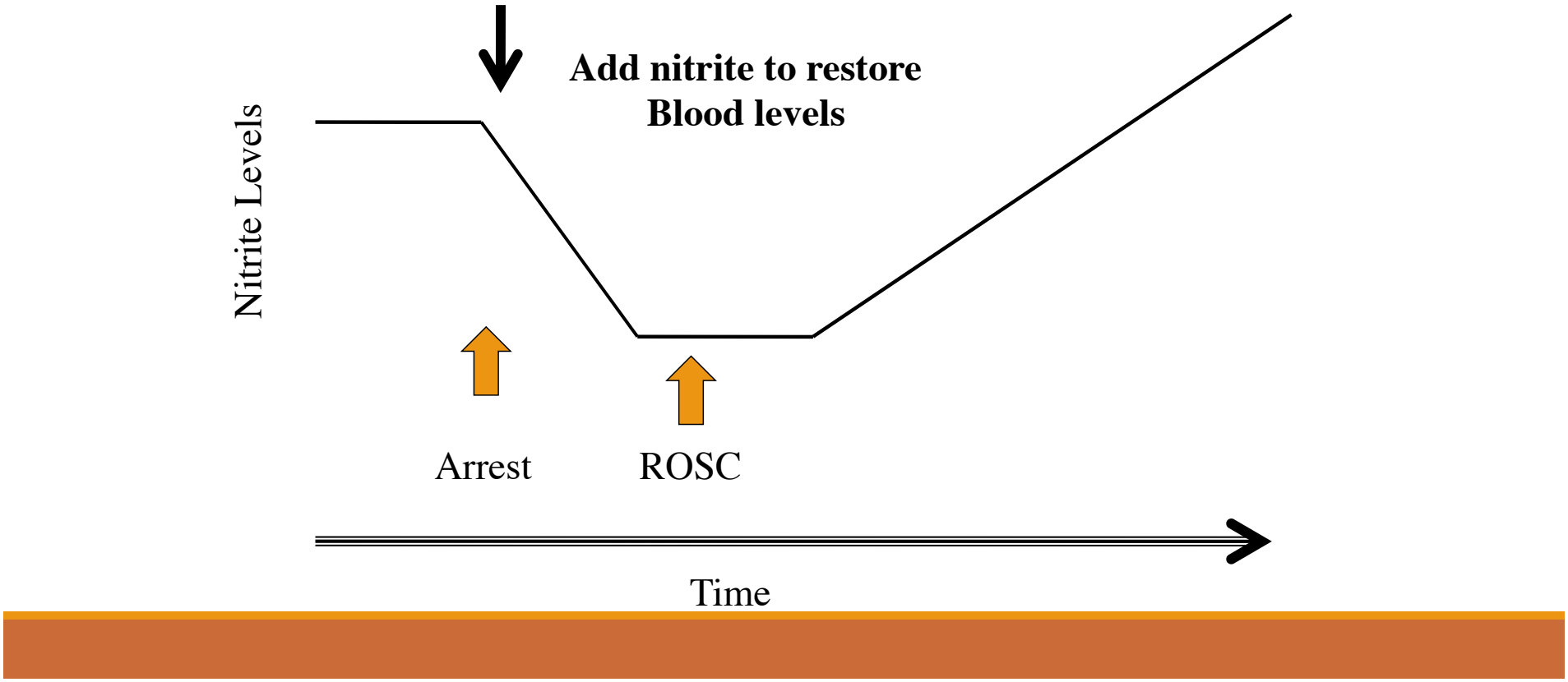
A Single Dose of Beetroot Juice Enhances Cycling Performance in Simulated Altitude

DAVID J. MUGGERIDGE[1,2], CHRISTOPHER C. F. HOWE[2], OWEN SPENDIFF[2], CHARLES PEDLAR[3], PHILIP E. JAMES[4], and CHRIS EASTON[1,2]

[1]Institute for Clinical Exercise and Health Science, University of the West of Scotland, Hamilton, Scotland, UNITED KINGDOM; [2]School of Life Sciences, Kingston University, Kingston upon Thames, England, UNITED KINGDOM; [3]School of Sport, Health and Applied Science, St Mary's University College, Twickenham, England, UNITED KINGDOM; and [4]Wales Heart Research Institute, Cardiff University School of Medicine, Cardiff, Wales, UNITED KINGDOM

What happens to nitrite levels during cardiac arrest?




Add nitrite to restore
Blood levels
Nitrite Levels
Arrest
ROSC
Time

Mouse cardiac arrest model

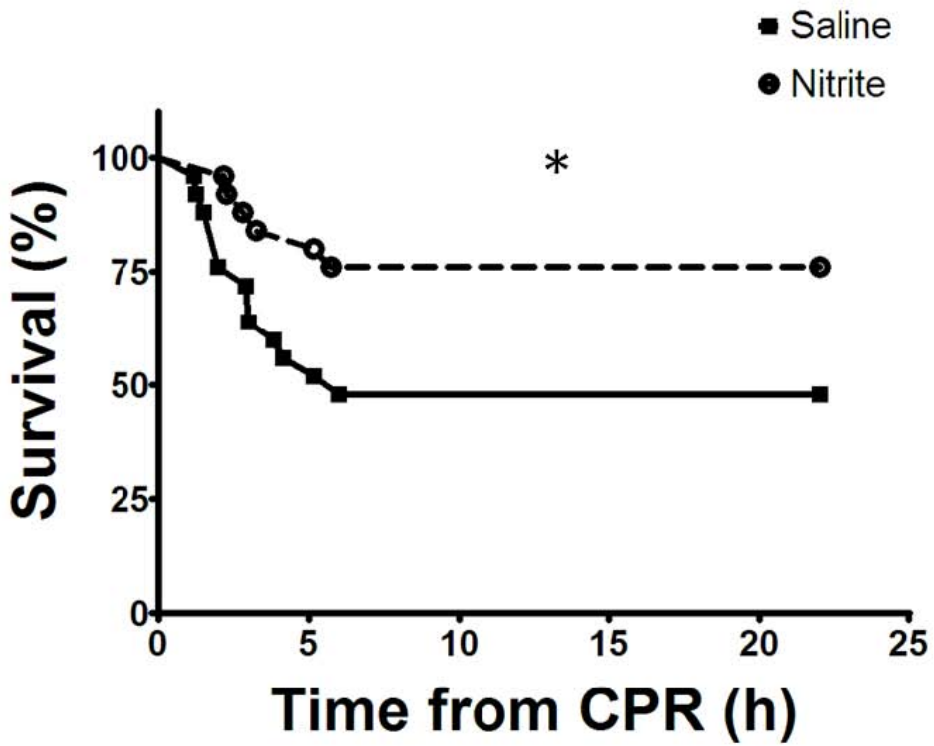


Figure 6. Nitrite therapy improves survival after cardiac arrest

After successful resuscitation, animals died between 1 and 6 hours after CPR. Nitrite therapy resulted in improved survival to 22 hours post-CPR compared to placebo (*, p=0.033; n=28/27 for placebo/nitrite groups).

SNOCAT Study Hypothesis

Infusion of sodium nitrite during resuscitation (before ROSC) will improve neurologic outcome and survival after cardiac arrest.

SNOCAT: Sodium nitrite out of hospital cardiac arrest trial

Phase 1 (dose finding and safety trial)

- n=100, expect 40 to survive to ED admission
- Open label, start dose of 25 mg.
- Achieve plasma level of 10 uM?

Eligibility

Out-of-hospital cardiac arrest (VF, non-VF)

Unconscious/not following commands

IV access/IO

Not in the three P's: Pregnant, Pediatric, Prisoners

Safety Data Being Collected

Re-arrest

Use of vasopressors: norepinephrine or epinephrine infusions

Blood Draws for NO_2 levels at ED or in field

- For Harborview Medical Center only additional draws at 20, 40, 60, 80, 100, 120 minute time points

Endpoints

Plasma level of nitrite at hospital, ED arrival

Safety: re-arrest, use of pressors

N=100 (expect 40 to be admitted to ED)

SNOCAT: Sodium nitrite out of hospital cardiac arrest trial

Phase 2 (safety and efficacy)

- n=1000, expect 400 to survive to ED
- Randomized/blinded
- Primary endpoint: Survival to ED (safety endpoint)
- Secondary endpoint: Survival to discharge

SNOCAT Investigators

Francis Kim

Peter Kudenchuk

Graham Nichol

Michele Olsufka

Michael Sayre

Sue Scruggs

Chuck Maynard

Susanne May

Safety

Low risk for hypotension

No risk for methemoglobin

“Restores nitrite level to baseline”

Given post-arrest at doses up to 9 mg, no significant effects

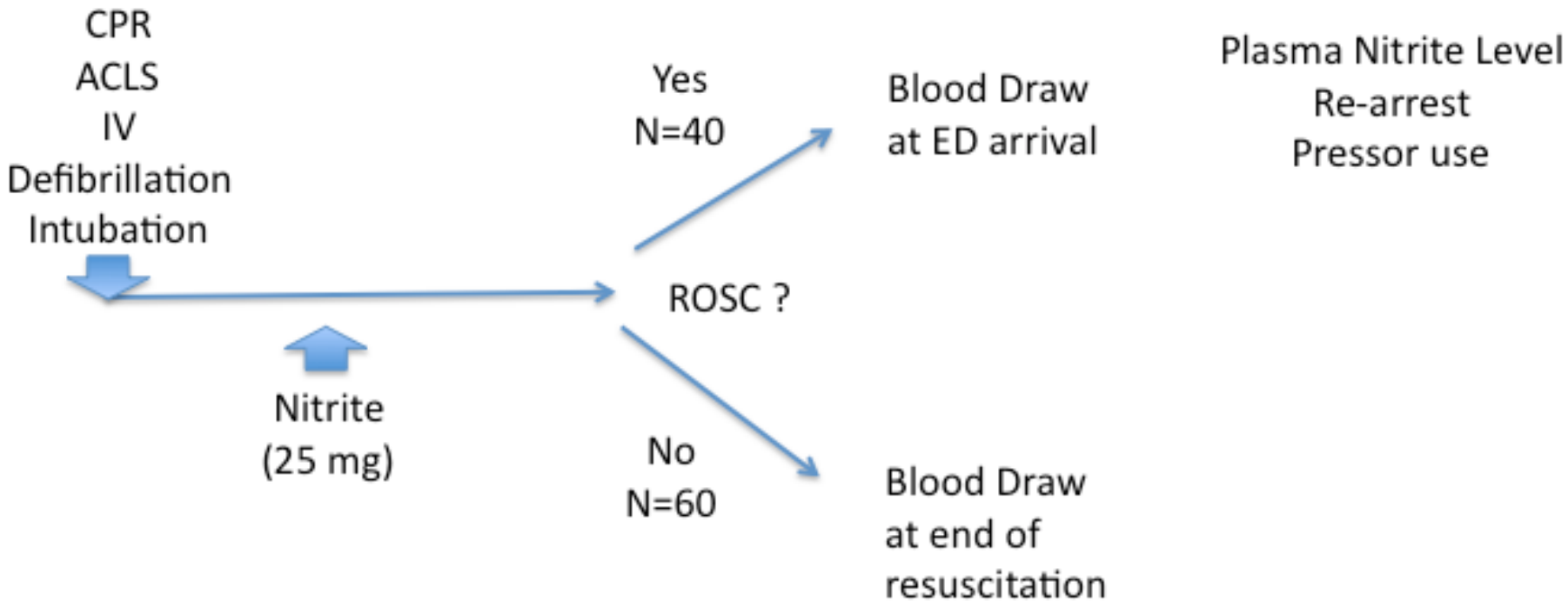
Effect during resuscitation unknown?

The good

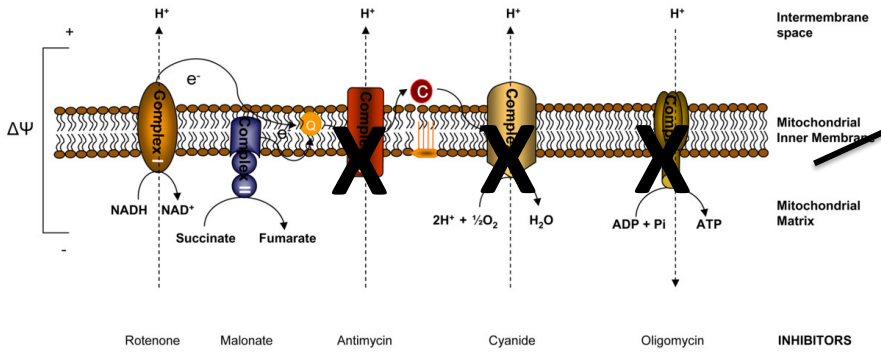
Increases NO levels in blood (blood pressure lowering effects)

May protect blood vessels

Found in supplements (increase endurance)


CPR
ACLS
IV
Defibrillation
Intubation
Nitrite
(25 mg)
ROSC ?
Yes
N=40
No
N=60
Blood Draw
at ED arrival
Blood Draw
at end of
resuscitation
Plasma Nitrite Level
Re-arrest
Pressor use

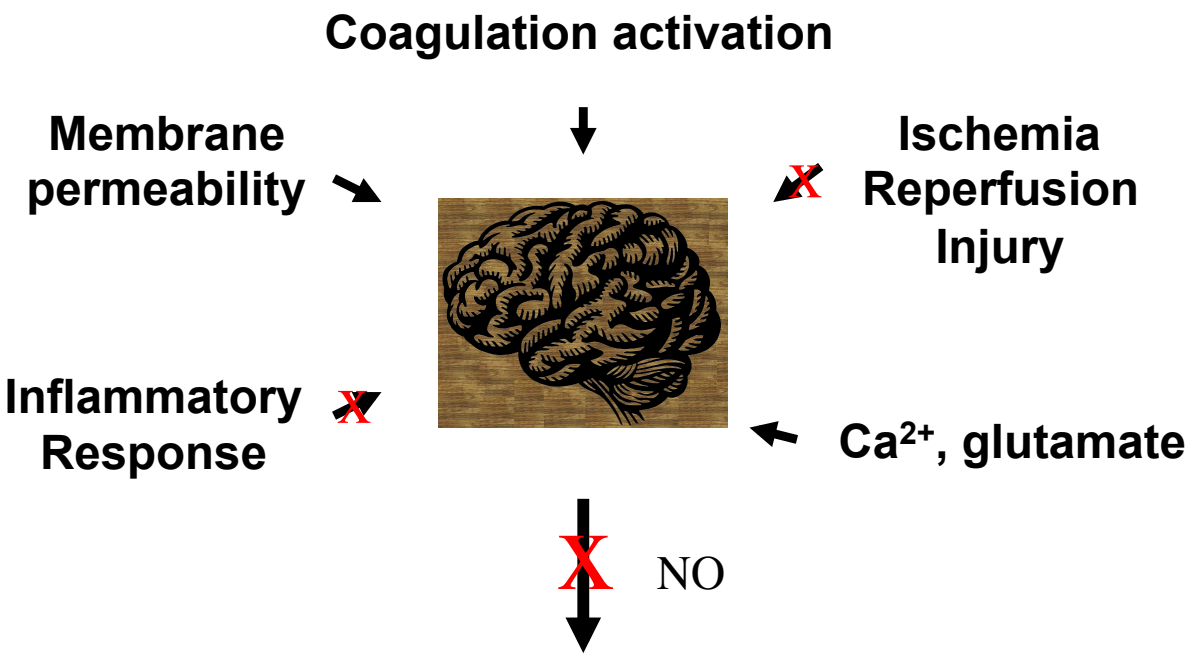
Ischemia/reperfusion



Superoxide

Nitric oxide
Hydrogen sulfide
Carbon monoxide

	NO	CO	H_2S
Toxic Gas?	Exhaust, air pollution	Air pollution	Sewers, swamps
Produced by cells	Nitric oxide synthase (NOS) nitrite	Made from hemoglobin	Synthesized from L-cysteine
Vascular effects	Vasodilates	Vasodilates	Vasodilates
Anti-inflammatory effects	Yes	Yes	Yes
Mitochondrial	Decrease	Decrease	Decrease


Coagulation activation
Membrane permeability
Ischemia Reperfusion Injury
Inflammatory Response
Ca2+, glutamate
NO
Brain cell injury/death

NO-ischemia

Protective role of nitric oxide in ischemia reperfusion (liver,heart, brain)

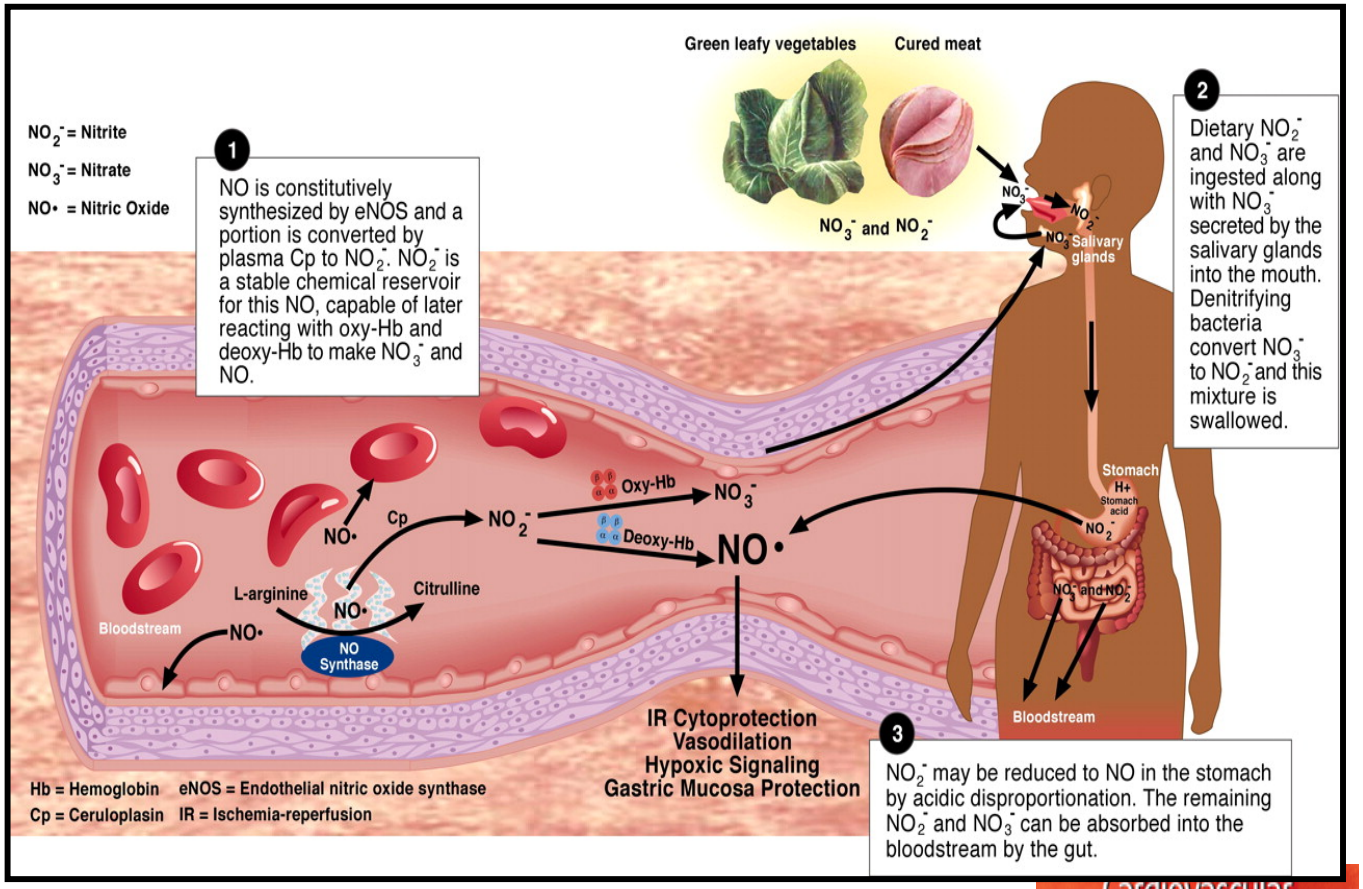
- Genetic overexpression studies
- Drug (NO-donor) (different structures)

NO production is reduced during ischemia

Nitric oxide production by NOS requires oxygen (not suitable for ischemia)

Nitric oxide production requires cofactors (limited during ischemia)

The NO-nitrite-nitrate pool



Dezfulian, C. et al. Cardiovasc Res 2007 75:327-338;
doi:10.1016/j.cardiores.2007.05.001

Cardiovascular Research

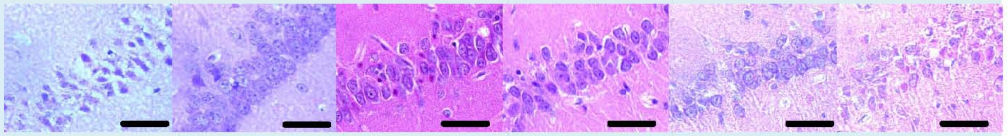
	Mouse 12 min asystolic arrest 3d post-arrest histology (n=3)		Rat 8 min asphyxial arrest 7d post-arrest histology (n=3)		Rat 8 min asphyxial arrest 7d post-arrest histology (n=6)	
Sample H&E histology; CA1 region of hippocampus						
Dose Delivered (μmol/kg)	Placebo	1.85	Placebo	13.3	Placebo	53.2
Pre-arrest Blood Nitrite (μM)	1.146 ± 0.213 (*; n=5)	1.146 ± 0.213 (*; n=5)	0.981 ± 0.833 (n=3)	0.811 ± 0.134 (n=3)	1.082 ± 0.340 (n=6)	1.133 ± 0.347 (n=6)
Post-arrest (pre-drug) Blood Nitrite (μM)	-	-	0.937 ± 0.741	0.904 ± 0.135	1.150 ± 0.381	0.836 ± 0.189
Post-arrest (post-drug) Blood Nitrite (μM)	0.644 ± 0.137	1.014 ± 0.136 (‡)	0.798 ± 0.398	25.835 ± 7.250 (‡)	0.953 ± 0.340	179.429 ± 53.974 (‡)
Neuronal Death (%)	57.7 ± 24.1	17.1 ± 5.7 (†)	50.3 ± 7.3	40.4 ± 10.1	15.1 ± 5.9	23.7 ± 8.6 (†)

Figure 3. Nitrite Therapy after Cardiac Arrest: Dose Titration with Brain Histology and Blood Nitrite Levels

Results of three separate studies examining different doses of nitrite given at the initiation of CPR (mice) or 5 minutes after the start of CPR as a 20 minute infusion (rats). In the mouse studies, * indicates that only a single blood draw was performed, pre-arrest levels are derived from a single sham group that did not receive cardiac arrest and there is no post-arrest pre-drug level since the drug was given at the initiation of CPR. In the hematoxylin and eosin stained brain slices, the bar indicates 40 micrometer distance. †, indicates $p<0.05$ and ‡ indicates $p<0.01$. Note that nitrite depletion was seen in the mouse but not rat models. Consistent with other animals studies, the low and moderate doses of nitrite which produced blood levels of 1 and 25.8 uM appear to be neuroprotective but not the highest dose which appeared to cause harm.

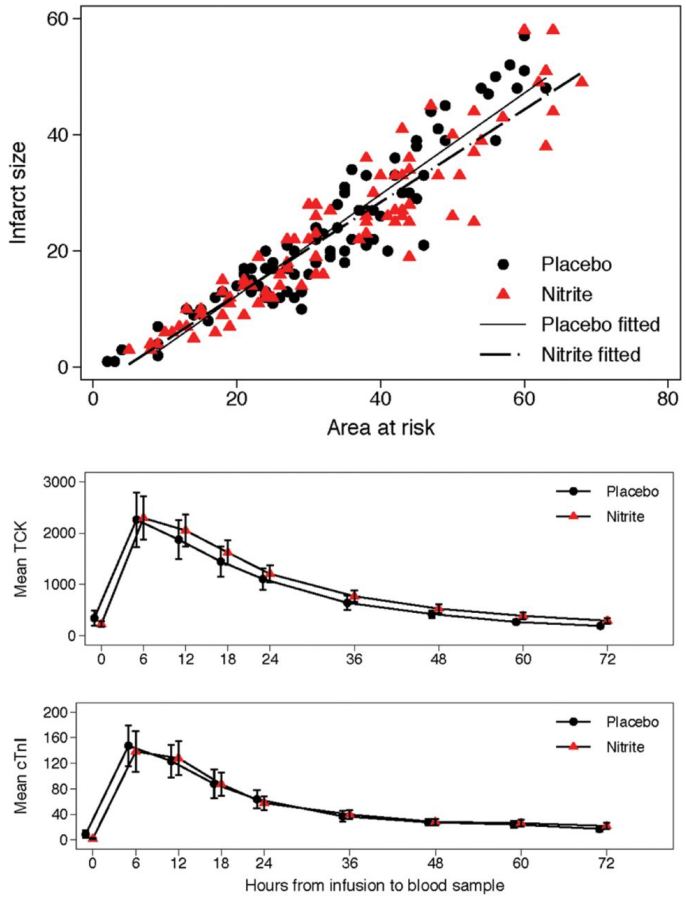
IV nitrite in acute ST elevation MI

229 pts randomized (70 uM, 5 mg over 5 minutes) or placebo before coronary intervention

Mean nitrite level at randomization (.70 uM)

Nitrite (1.42 uM) vs. placebo (.18 uM) 5 min after completion of infusion

Siddiqu N, European Heart Journal 2014



Siddiqi N et al. Eur Heart J 2014;35:1255-1262

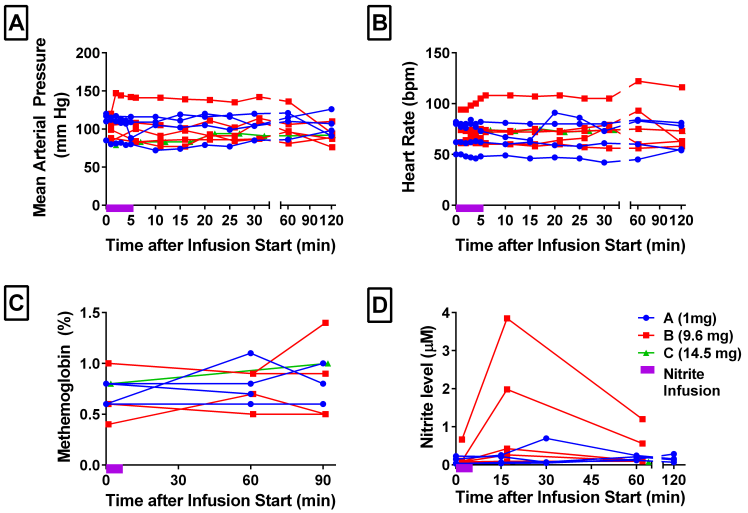
Clinical-nitrites

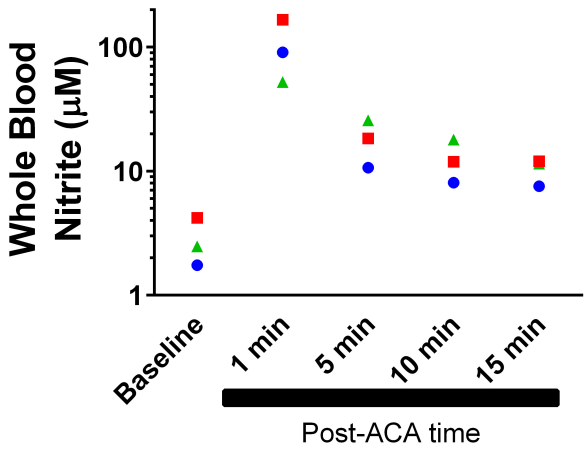
Peripheral arterial disease (oral doses 40-80 mg)-2014

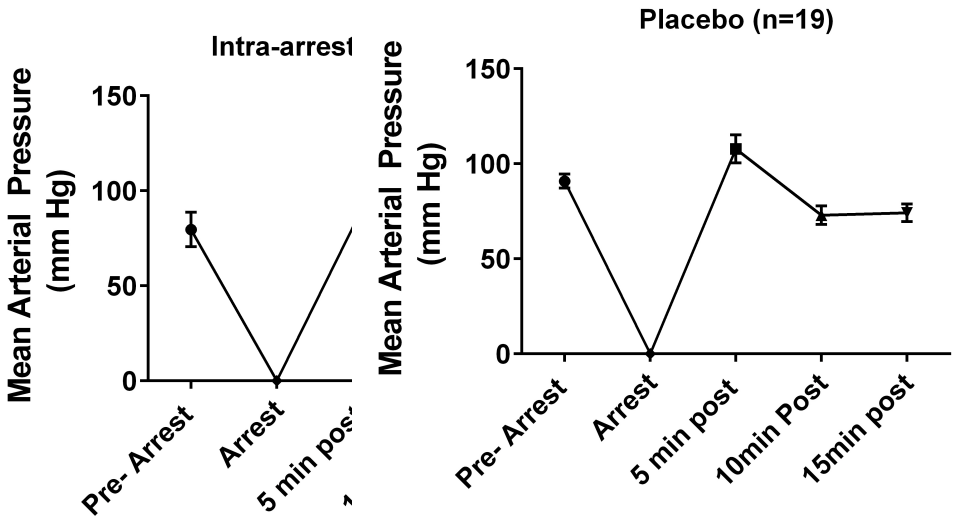
CHF (17.5 mg)-2015

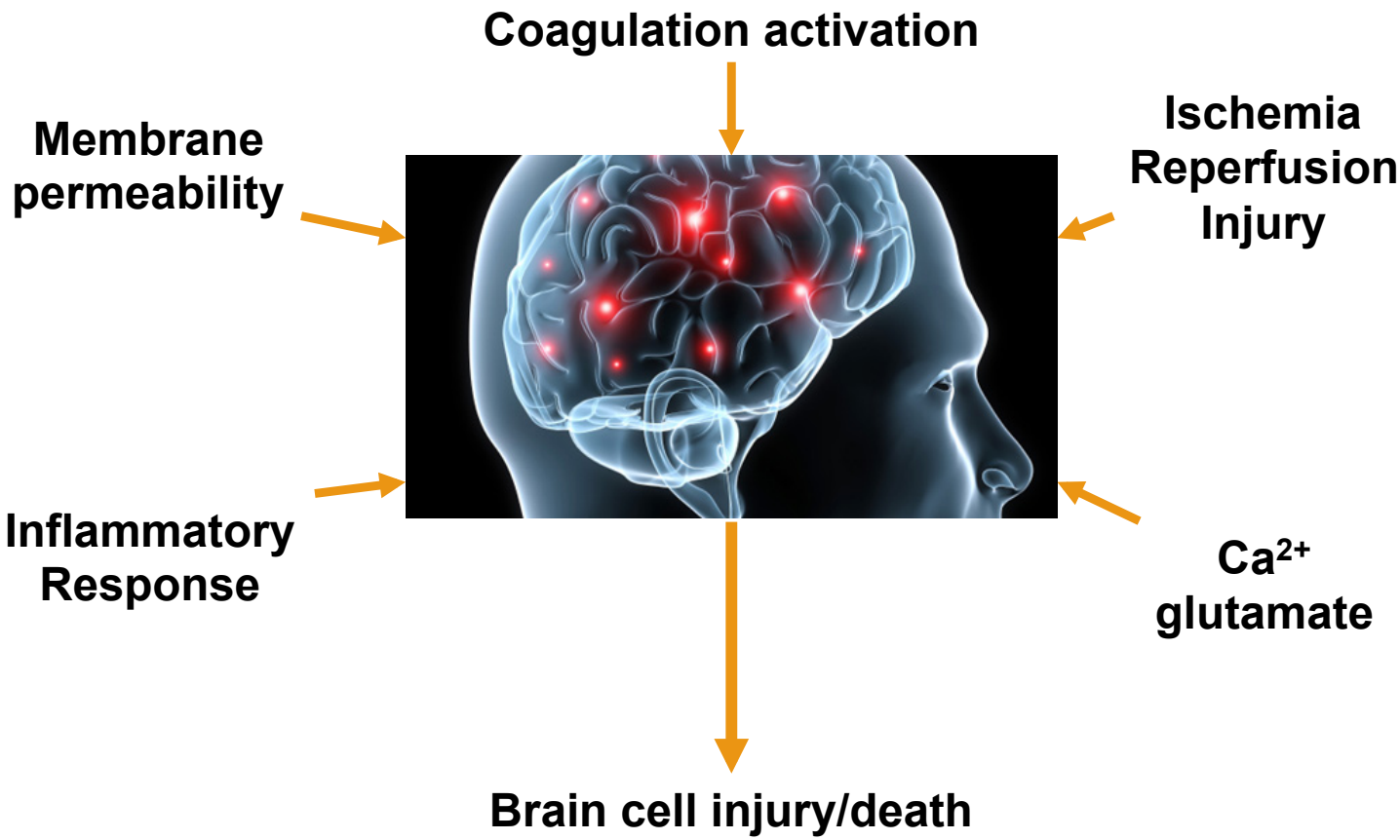
Organ preservation for transplant

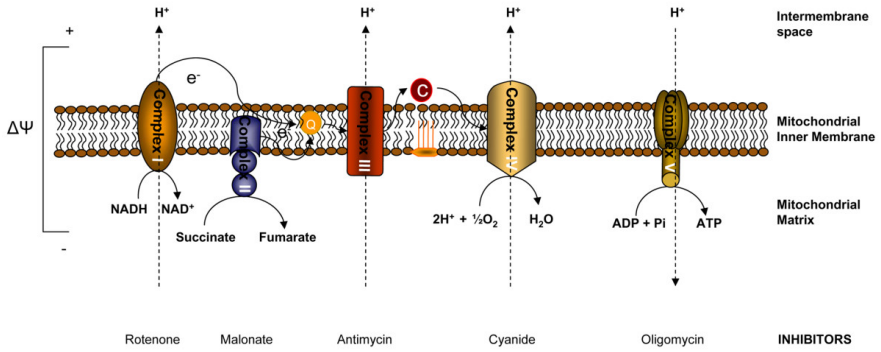
Cardiac arrest (post) (1-14 mg)


A
Mean Arterial Pressure (mm Hg)
200
150
100
50
0
0 5 10 15 20 25 30 60 90 120
Time after Infusion Start (min)
B
Heart Rate (bpm)
150
100
50
0
0 5 10 15 20 25 30 60 90 120
Time after Infusion Start (min)
C
Methemoglobin (%)
1.5
1.0
0.5
0.0
0 30 60 90
Time after Infusion Start (min)
D
Nitrite level (μM)
4
3
2
1
0
0 15 30 45 60 120
Time after Infusion Start (min)
A (1mg)
B (9.6 mg)
C (14.5 mg)
Nitrite Infusion

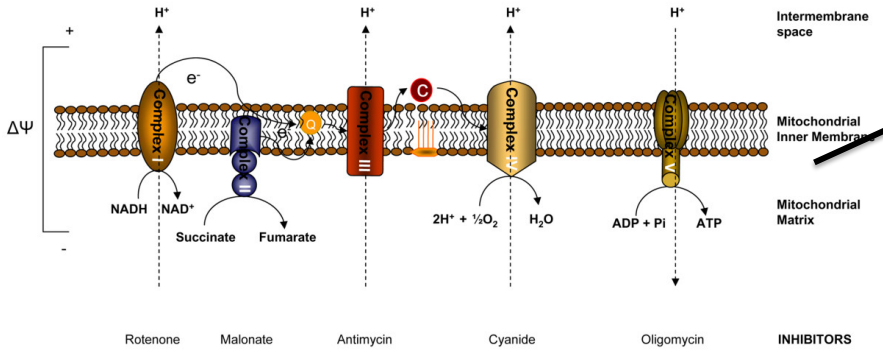

Whole Blood Nitrite (μM)
100
10
1
Baseline
1 min
5 min
10 min
15 min
Post-ACA time


Intra-arrest
Mean Arterial Pressure (mm Hg)
150
100
50
0
Pre- Arrest
Arrest
Placebo (n=19)
Mean Arterial Pressure (mm Hg)
150
100
50
0
Pre- Arrest
Arrest
5 min post
10min Post
15min post


Coagulation activation
Membrane permeability
Ischemia Reperfusion Injury
Inflammatory Response
Ca^{2+} glutamate
Brain cell injury/death

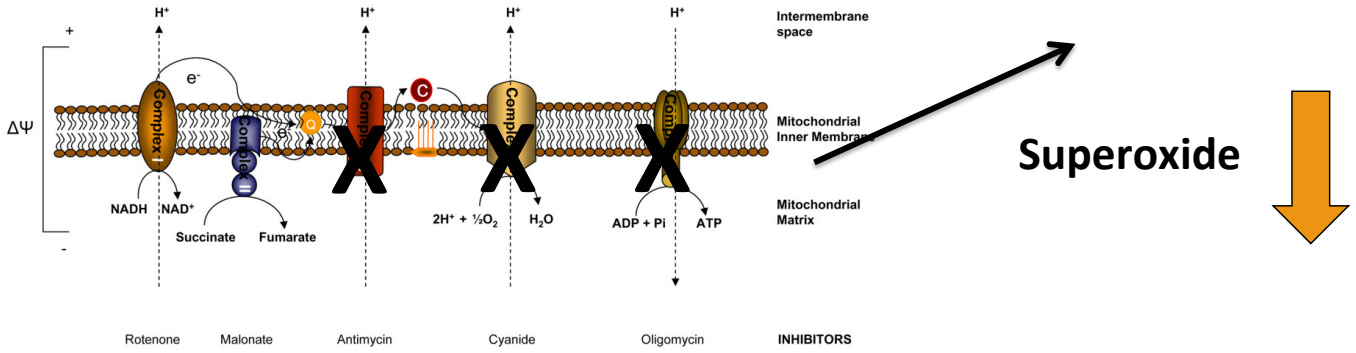

H+
H+
H+
H+
Intermembrane space
+
ΔΨ
-
e-
Complex I
Complex II
Complex III
Complex IV
Complex V
C
Mitochondrial Inner Membrane
Mitochondrial Matrix
NADH
NAD+
Succinate
Fumarate
2H+ + ½O2
H2O
ADP + Pi
ATP
Rotenone
Malonate
Antimycin
Cyanide
Oligomycin
INHIBITORS

Ischemia/reperfusion



Superoxide

Ischemia/reperfusion



Superoxide