

Einfluss von PETN auf das linksventrikuläre Remodeling nach experimentellem Myokardinfarkt



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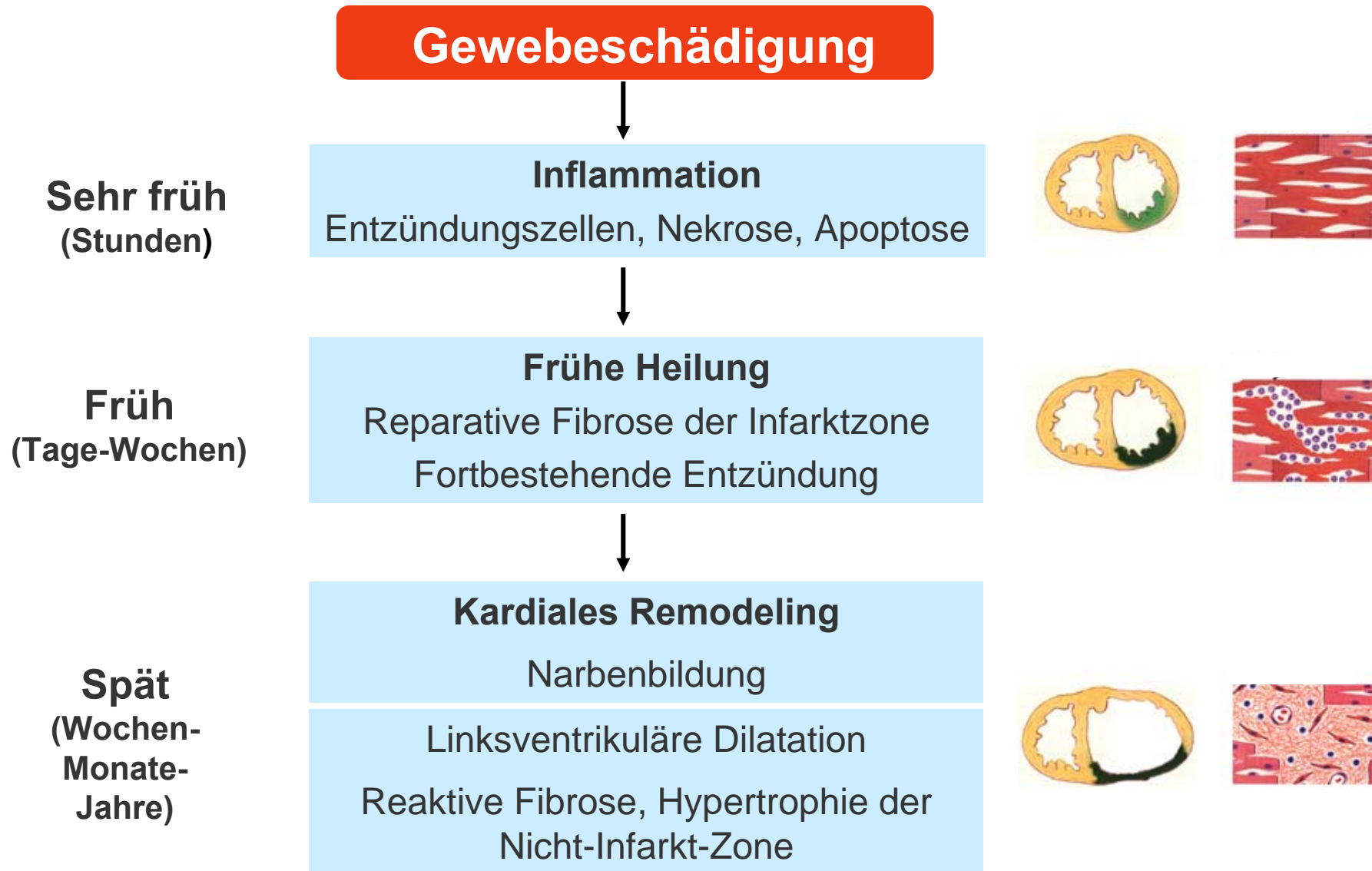
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Medizinische Hochschule Hannover

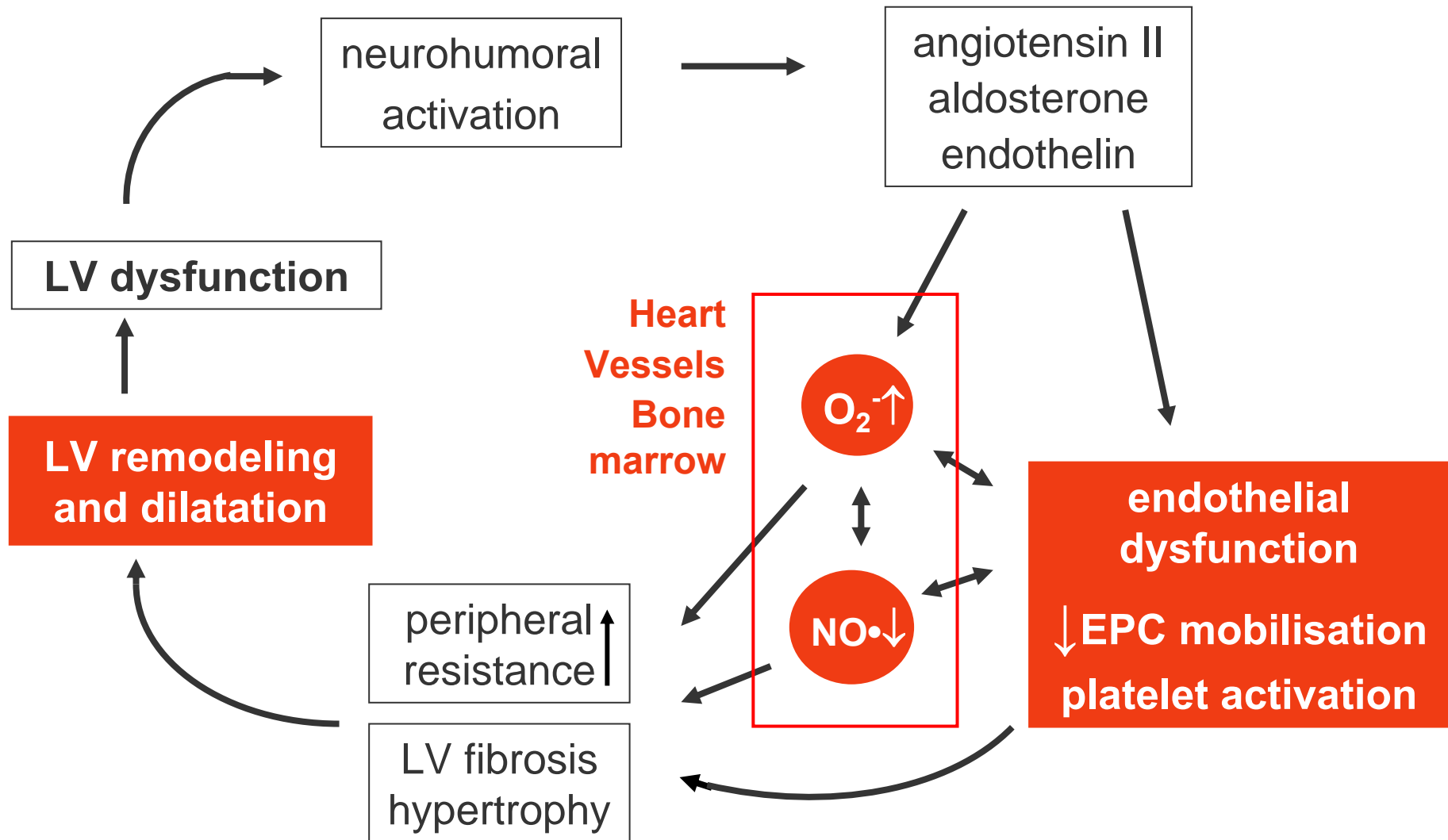
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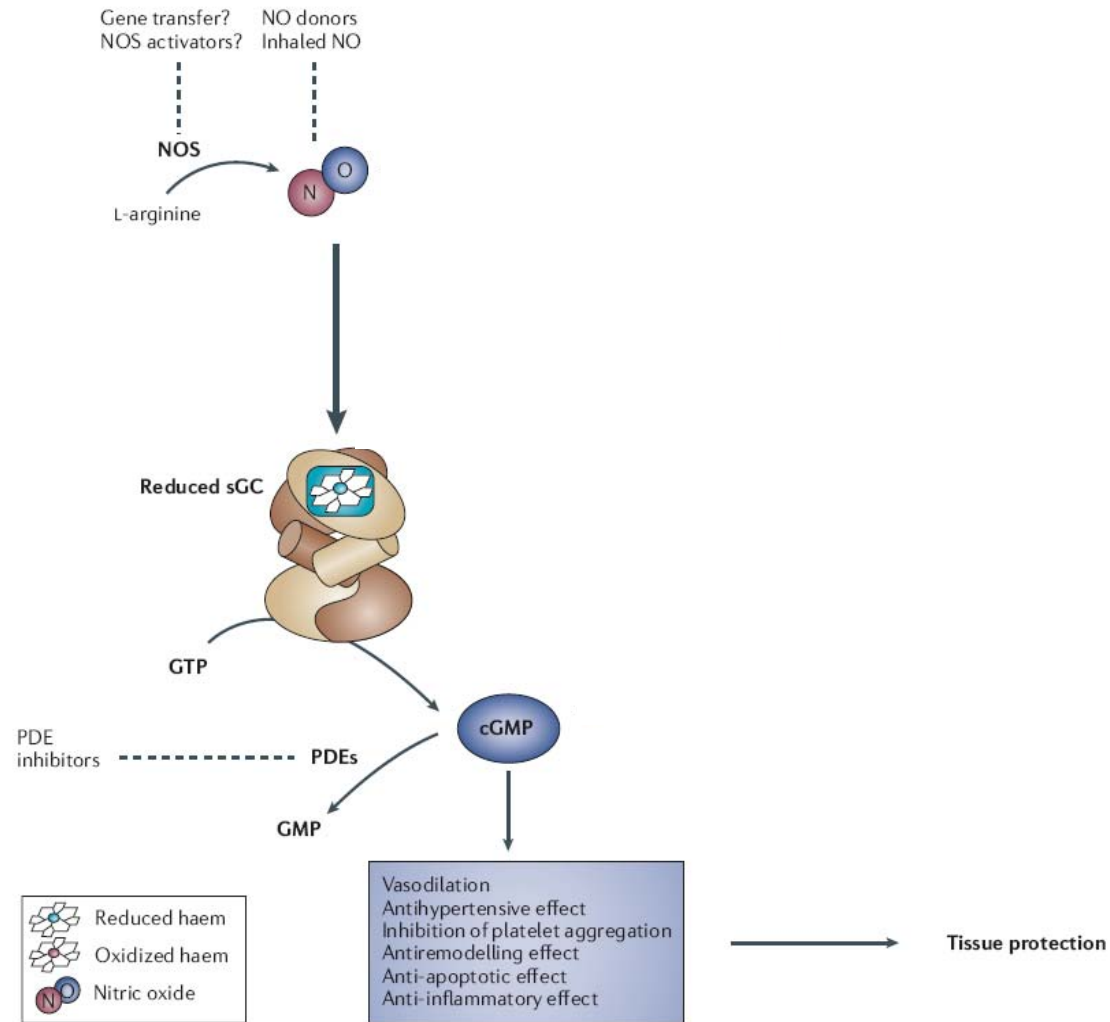
Heilung und Remodeling nach Myokardinfarkt



NO – superoxide balance in heart failure

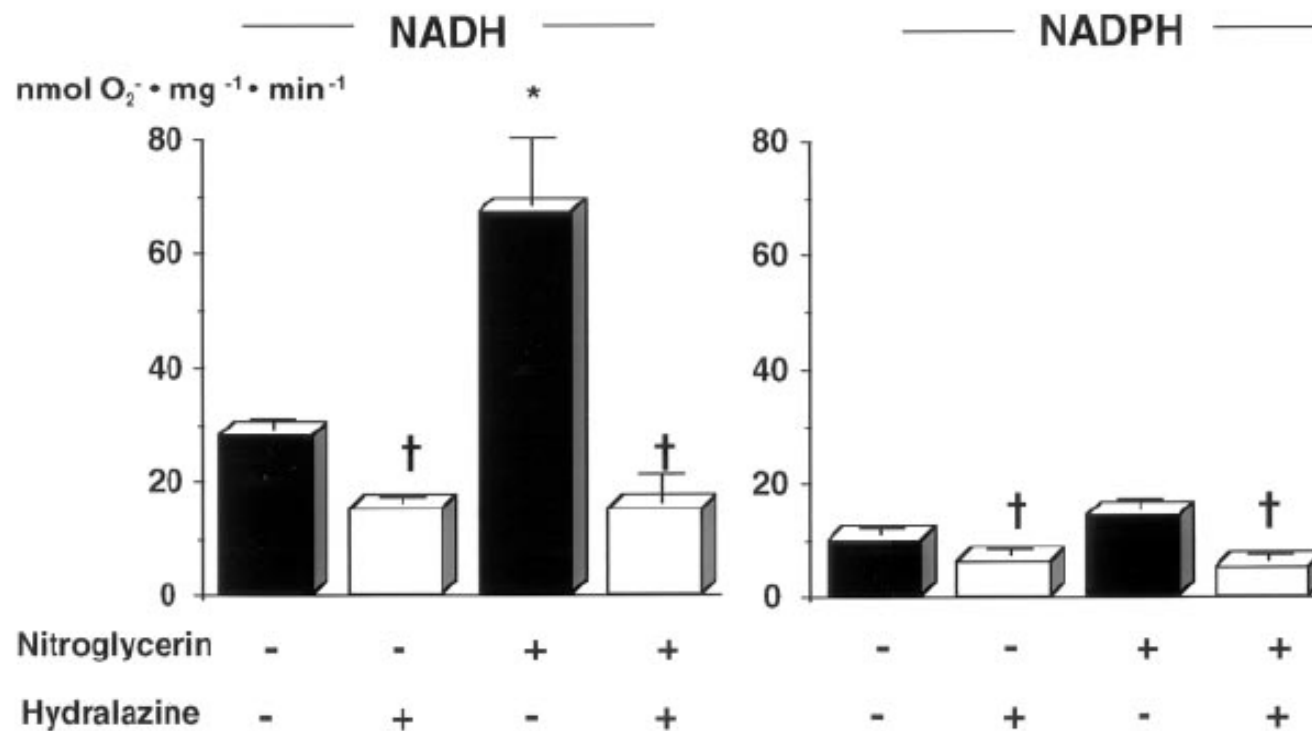


Problem der Peroxynitrit-Bildung



modifiziert
nach
Evgenov et
al., 2006

Aktivierung der vaskulären NADH/NADPH-Oxidase nach Nitrattherapie wird durch Hydralazin unterbunden



Münzel, JCI 1996

V-HeFT II: Enalapril vs. Hydralazin-ISDN Kombination bei chronischer systolischer Herzinsuffizienz

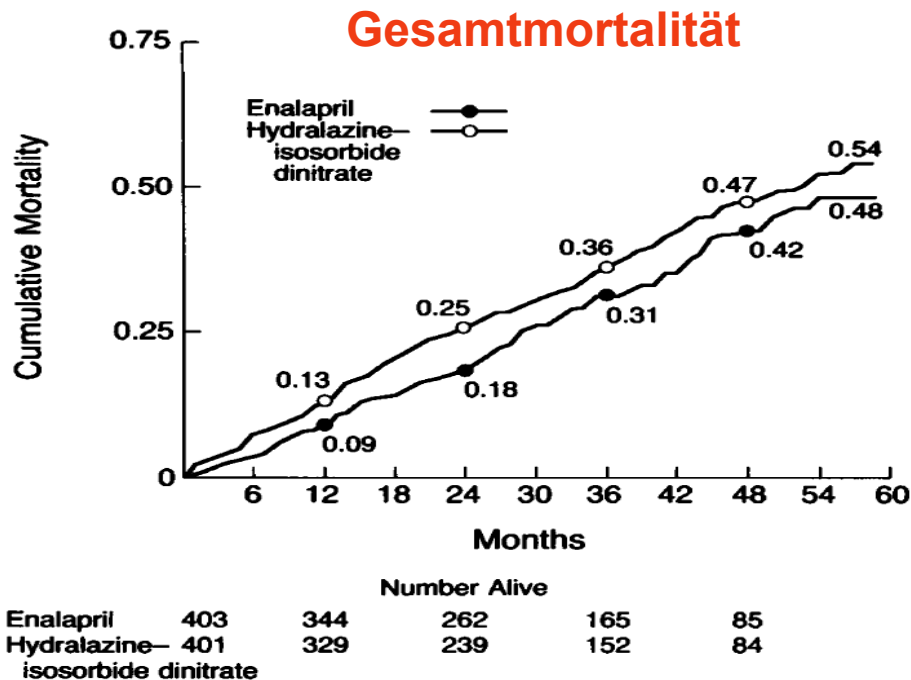


Figure 1. Cumulative Mortality in the Enalapril and Hydralazine–Isosorbide Dinitrate Treatment Arms over the Entire Follow-up Period.

Cumulative mortality rates are shown after each 12-month period. For the comparison of the treatment arms after two years and overall, $P = 0.016$ and $P = 0.08$, respectively (log-rank test). The number of patients alive after each year is shown below the graph.

Cohn JN et al.,
N Engl J Med 1991

V-HeFT II: Enalapril vs. Hydralazin-ISDN Kombination bei chronischer systolischer Herzinsuffizienz

Ejektionsfraktion

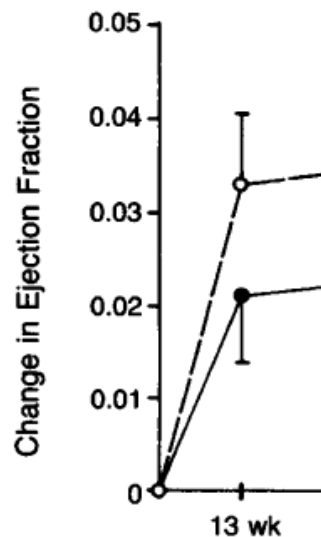
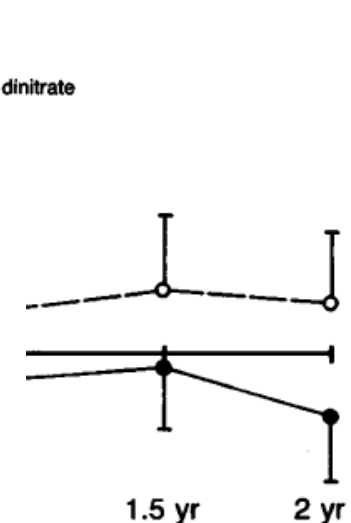


Figure 2. Mean Change in Ejection Fraction over the

Vertical bars represent 95 percent confidence intervals. The increase after the first 13 weeks in the hydralazine-isosorbide dinitrate arm was greater than in the enalapril arm ($P < 0.05$).

strengthen the conclusion that vasodilator therapy should be included in the standard treatment for heart failure. The different effects of the two regimens (enalapril and hydralazine-isosorbide dinitrate) on mortality and physiologic end points suggest that the profile of effects might be enhanced if the regimens were used in combination. (N Engl J Med 1991; 325:303-10.)

Sauerstoffaufnahme

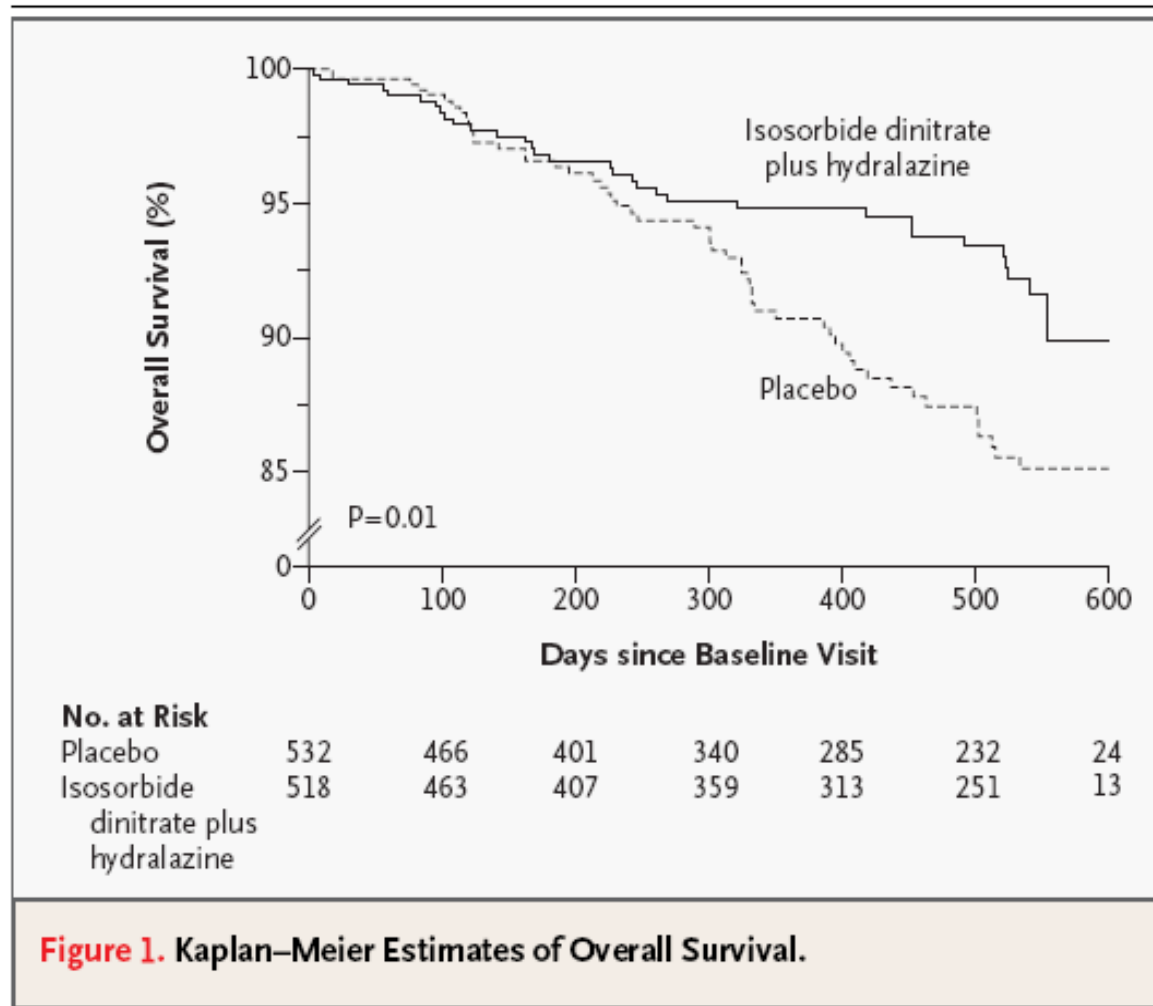


Change in Peak Oxygen Consumption of the Study in Each Arm.

The increase in the hydralazine-isosorbide dinitrate arm was significant for the first six months ($P < 0.01$) and was greater than in the enalapril arm.

Cohn JN et al., N Engl J Med 1991

Mortalitätsreduktion bei Afro-Amerikanern mit Herzinsuffizienz durch Nitrat/Hydralazin-Kombination

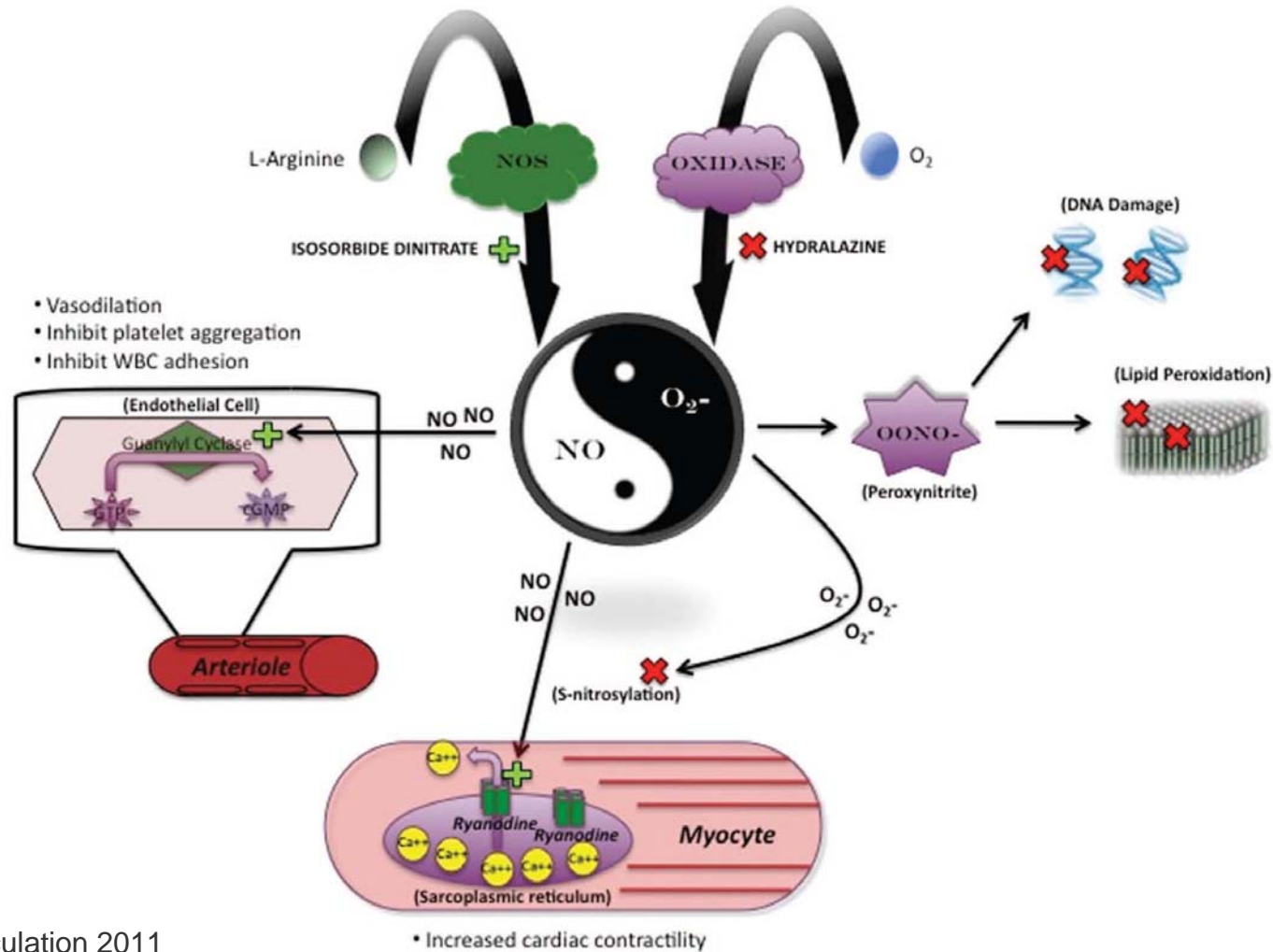


Taylor et al., NEJM 2004

Hydralazine and Isosorbide Dinitrate in Heart Failure

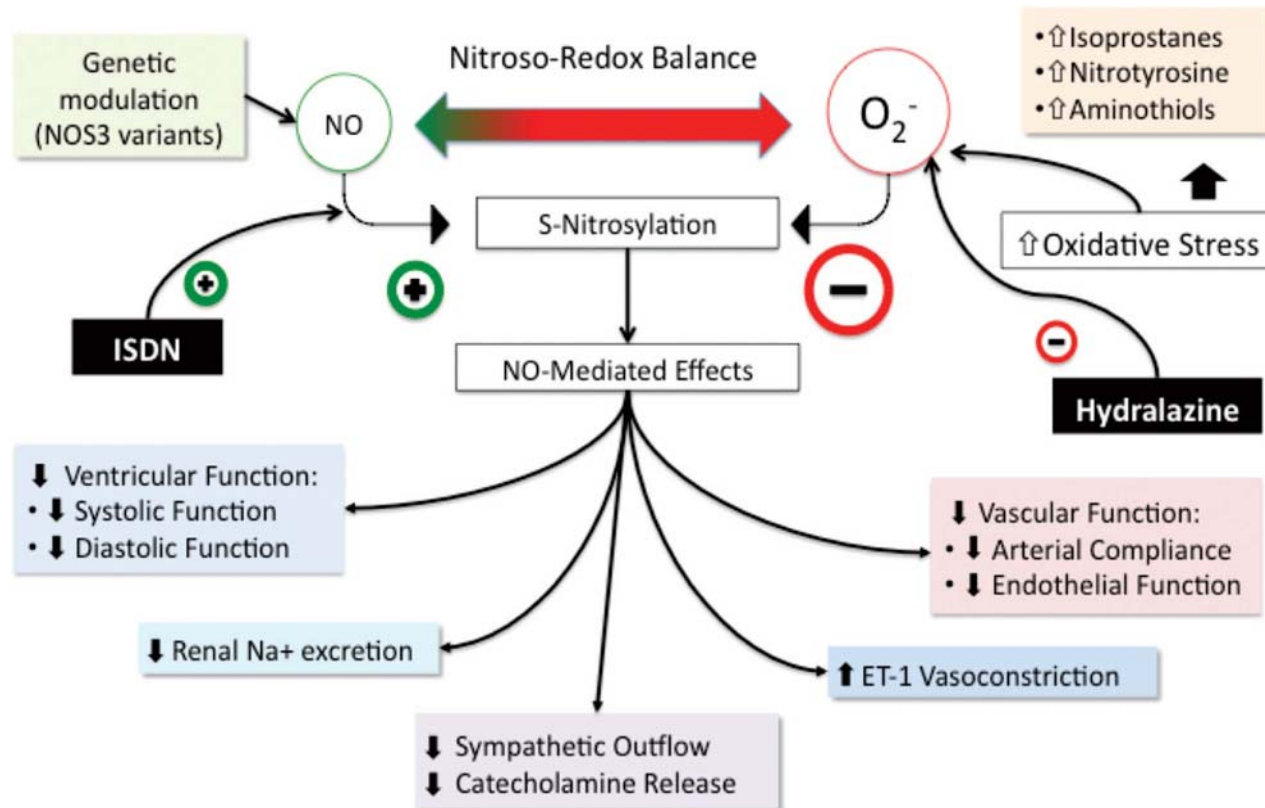
Historical Perspective, Mechanisms, and Future Directions

Robert T. Cole, MD; Andreas P. Kalogeropoulos, MD; Vasiliki V. Georgiopolou, MD;
Mihai Gheorghiane, MD; Arshed Quyyumi, MD; Clyde Yancy, MD; Javed Butler, MD, MPH



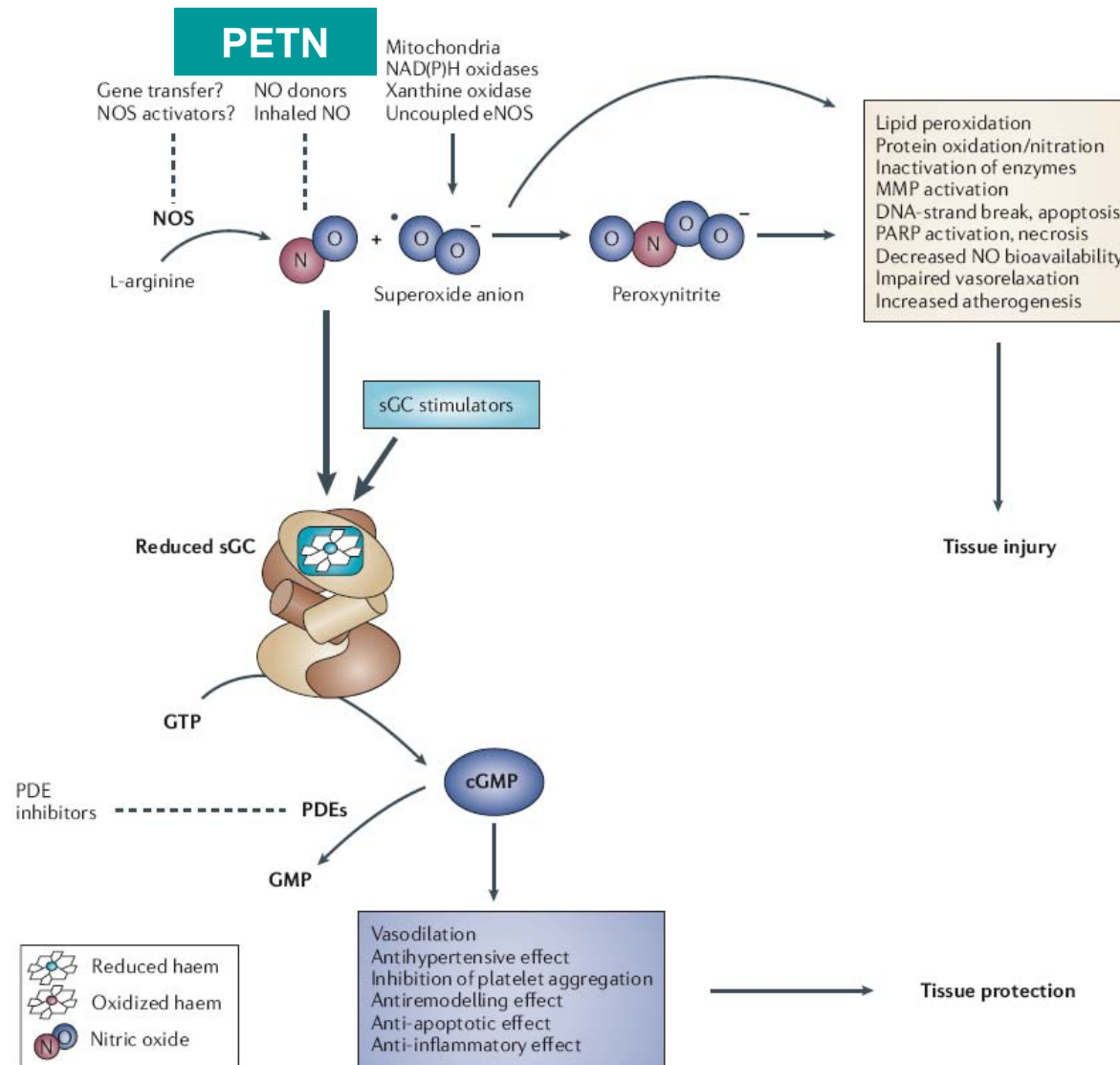
Cole et al. Circulation 2011

Effekte von Nitrat/Hydralazin-Kombination bei Herzinsuffizienz



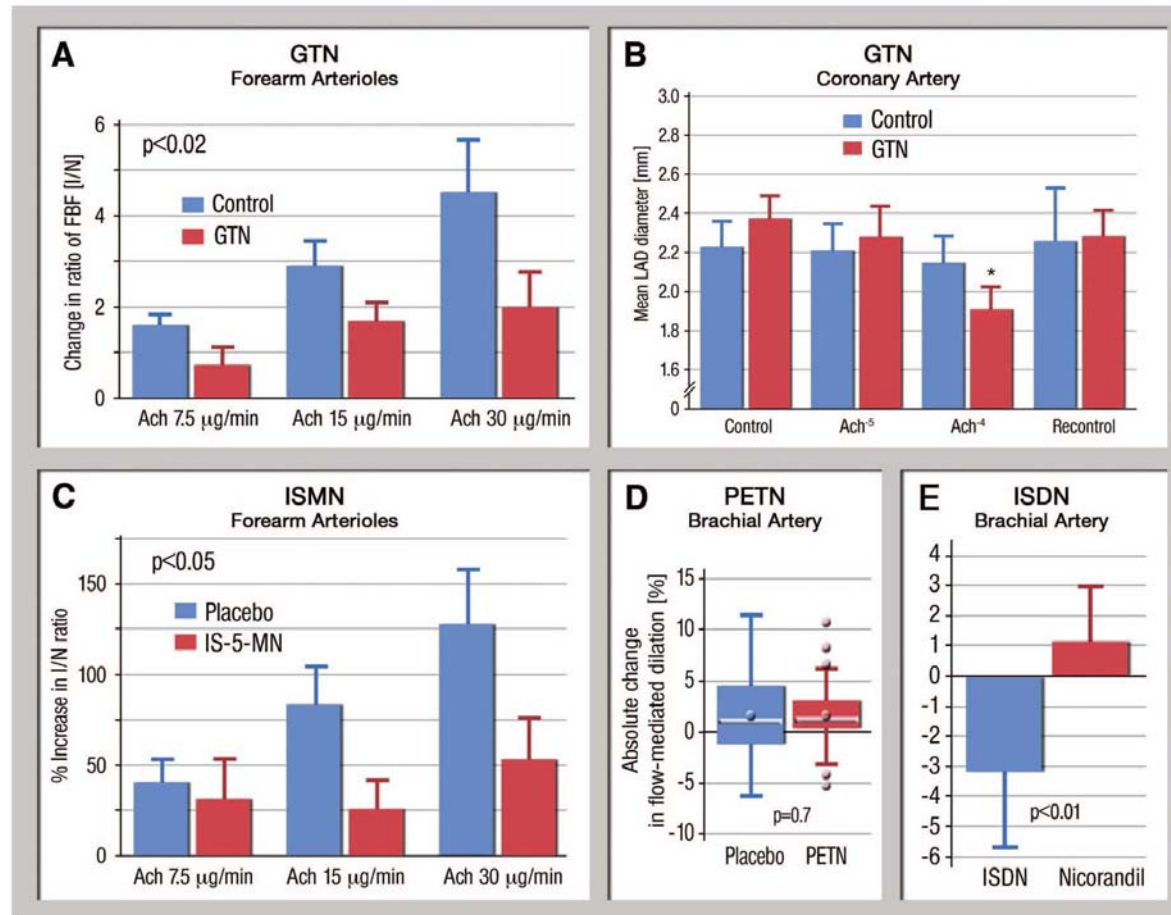
Cole et al. Circulation 2011

Oder doch einfach PETN?



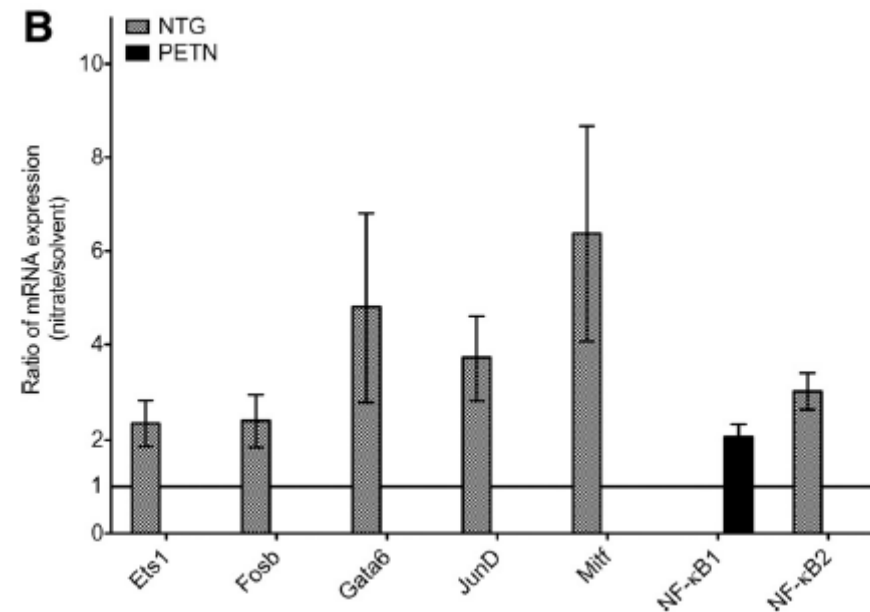
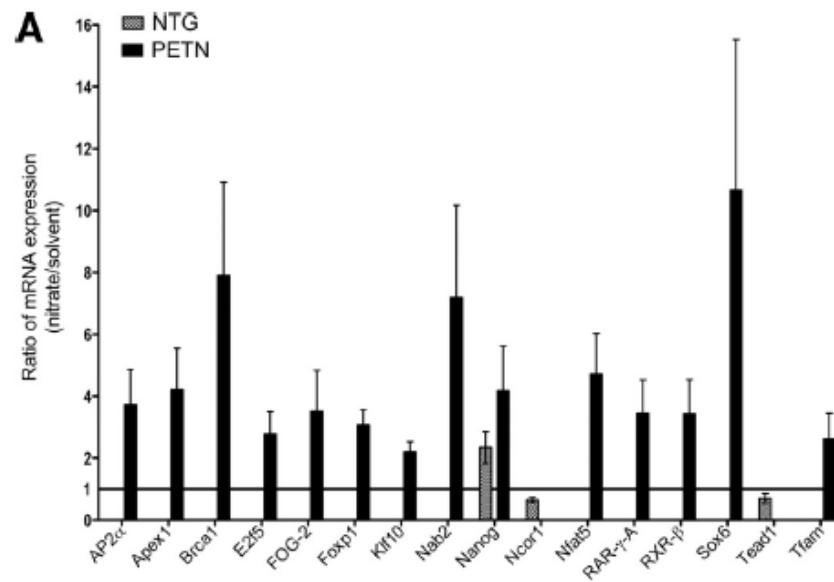
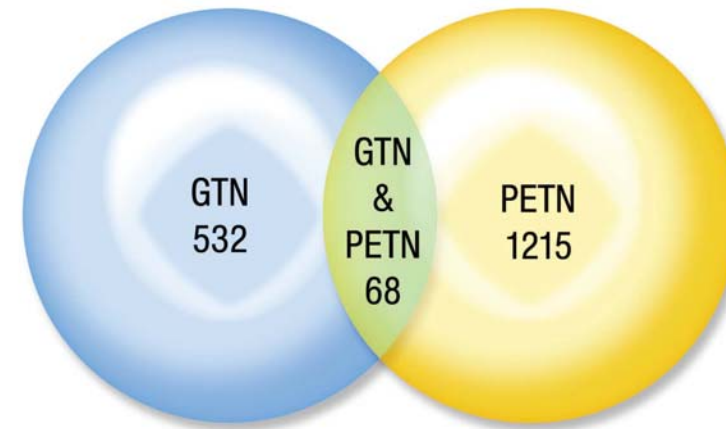
modifiziert
nach
Evgenov et
al., 2006

PETN-Therapie verursacht keinen oxidativen Stress und Endotheldysfunktion



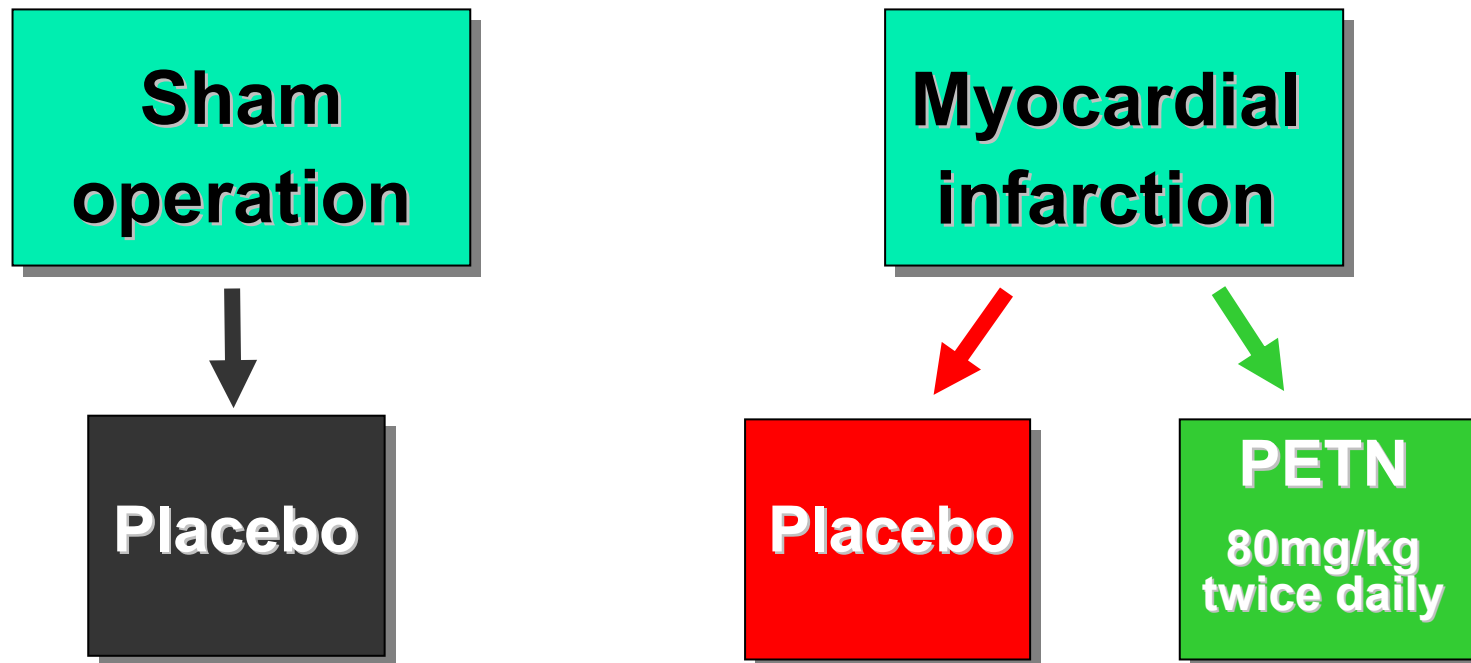
Münzel, Daiber, Gori, Circulation 2011

Änderungen der myokardialen Genexpression unter GTN- vs. PETN-Therapie



Pautz et al. *Physiol Genom* 2009; Münzel, Daiber, Gori, *Circulation* 2011

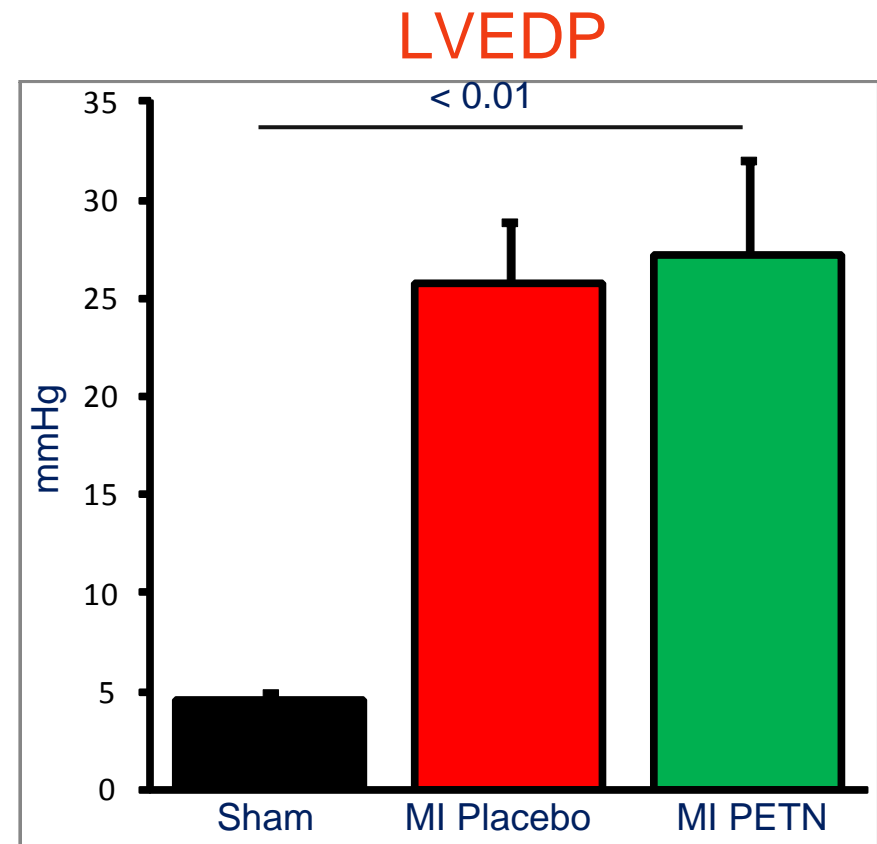
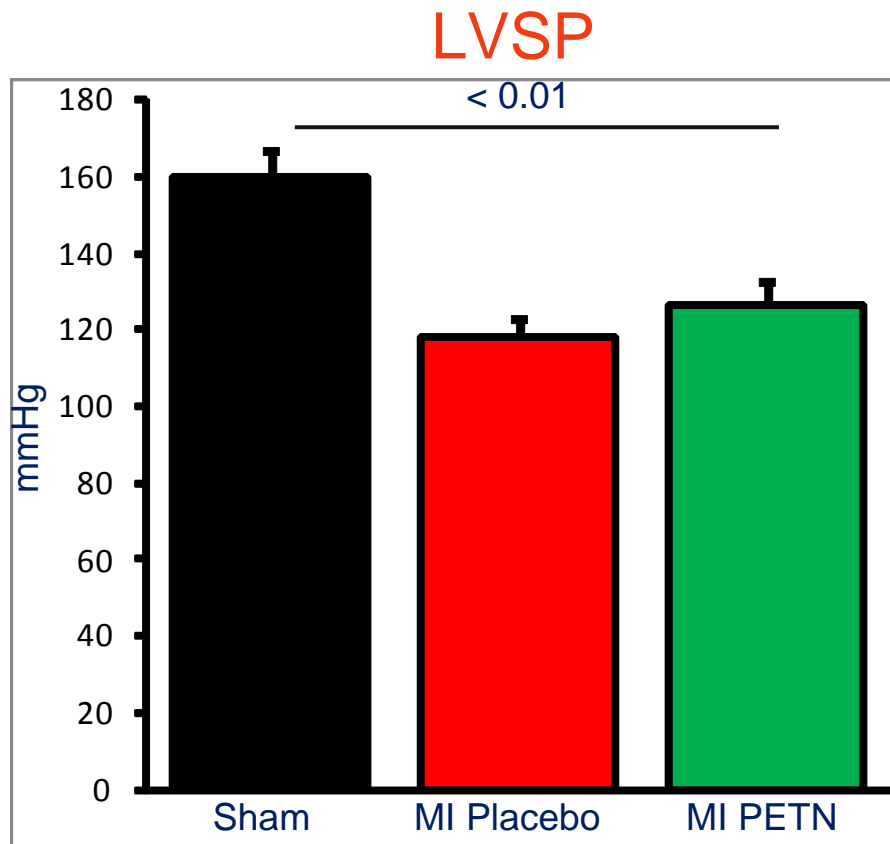
Treatment protocol



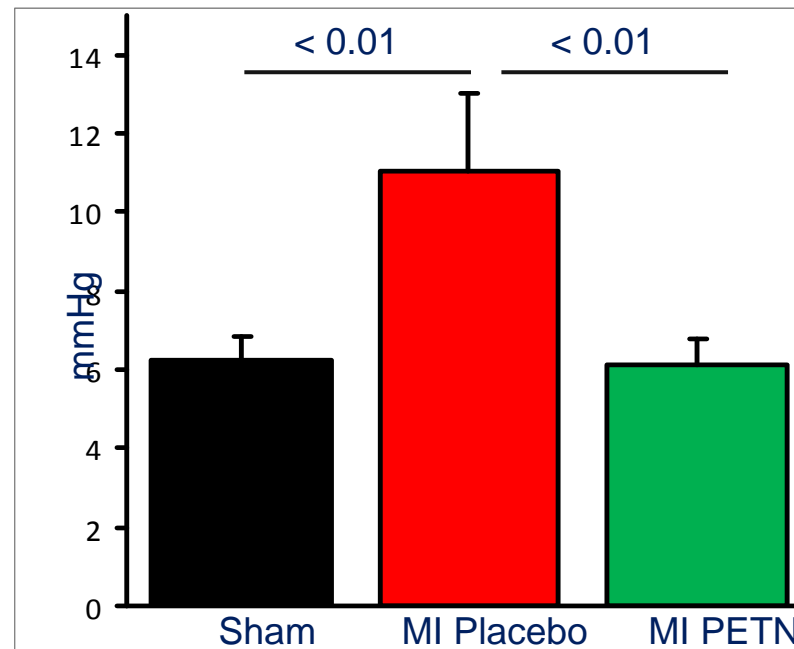
Treatment period: 9 weeks, starting on 7th day after MI

PETN post MI

- LV systolic and diastolic pressure -

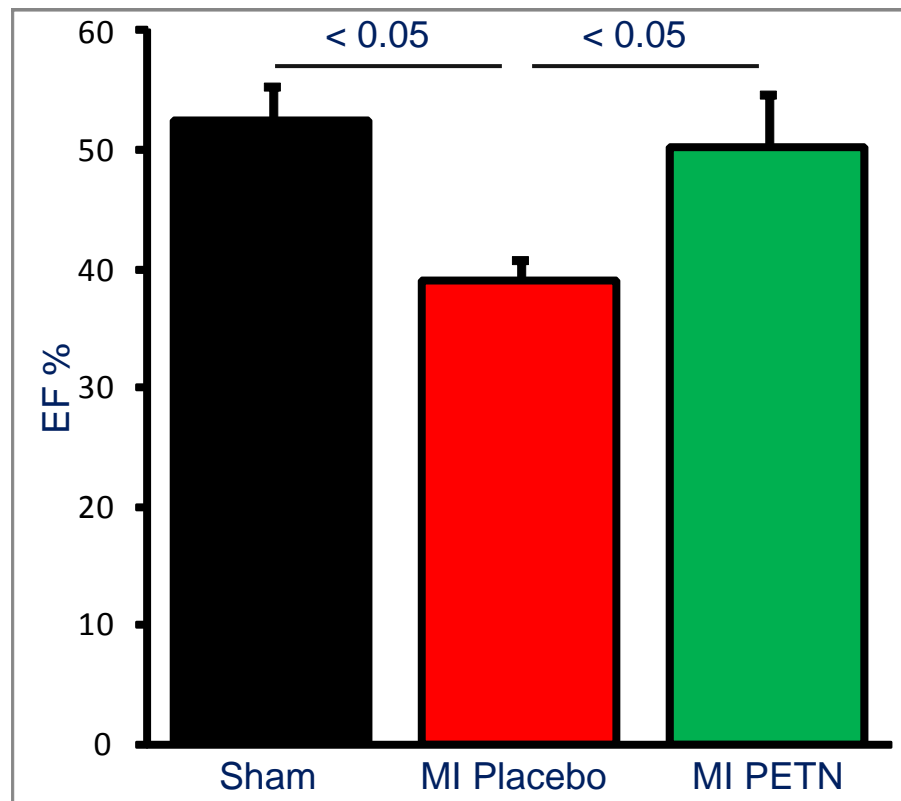
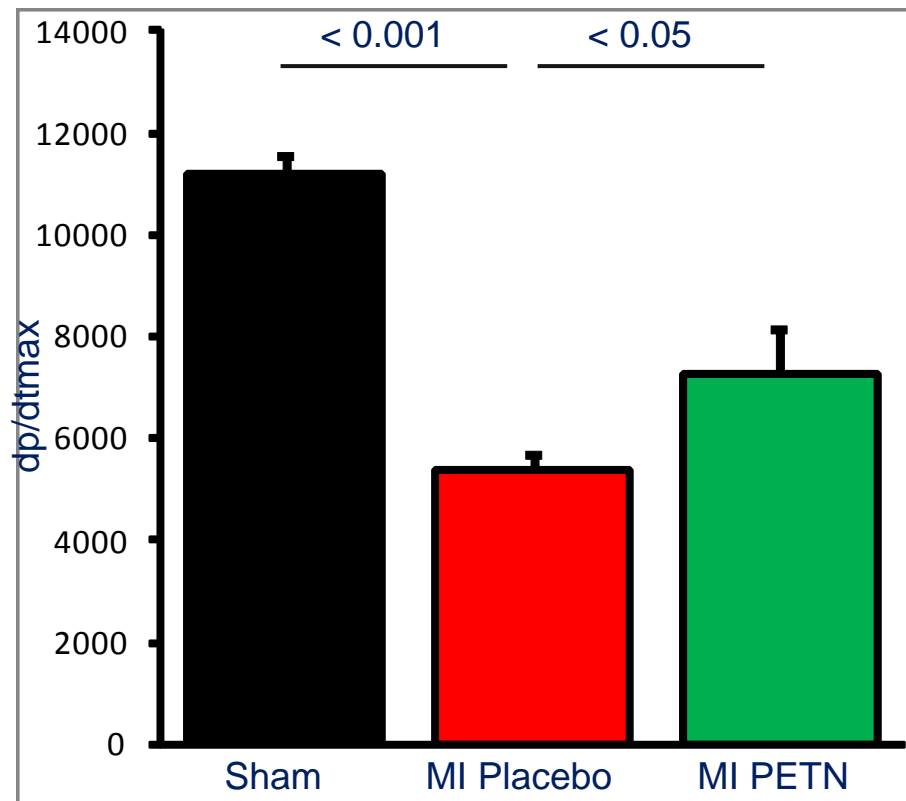


PETN post MI - RA pressure -



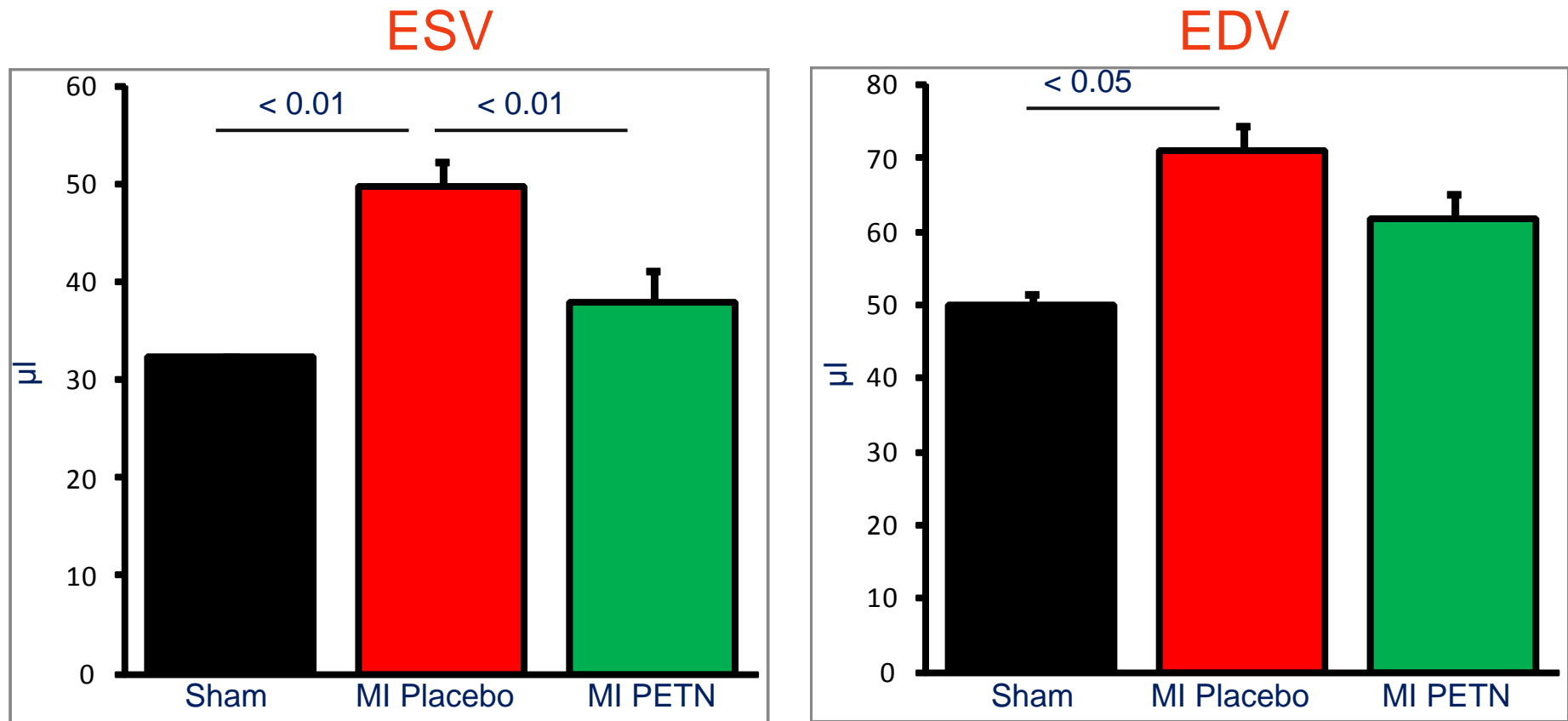
PETN post MI

- LV contractility and ejection fraction -

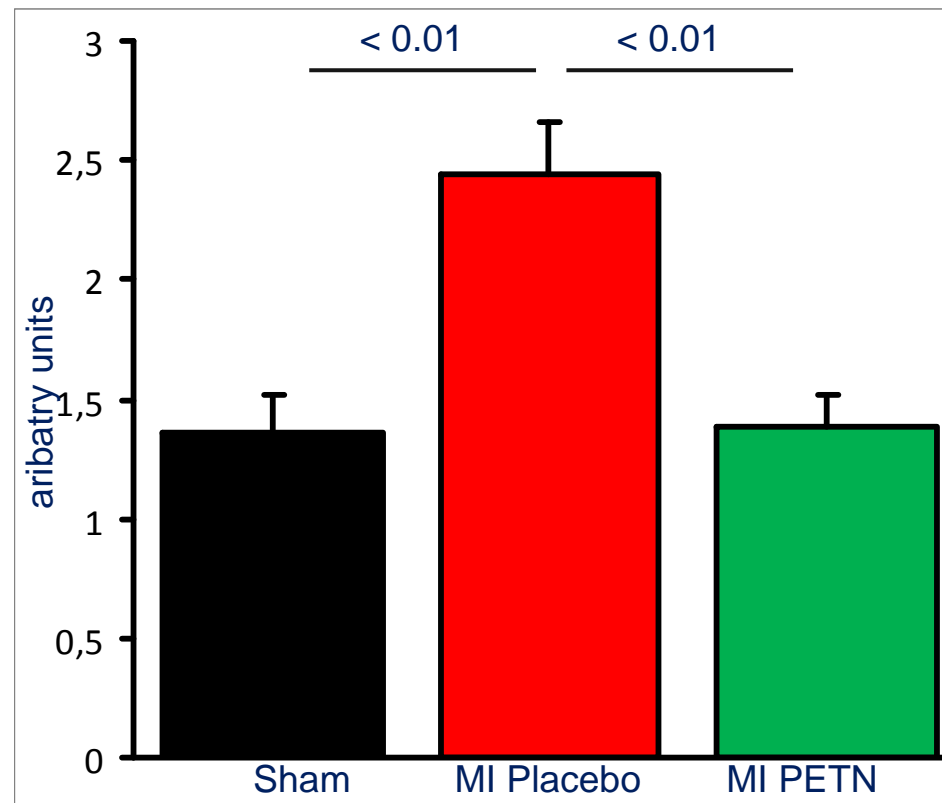
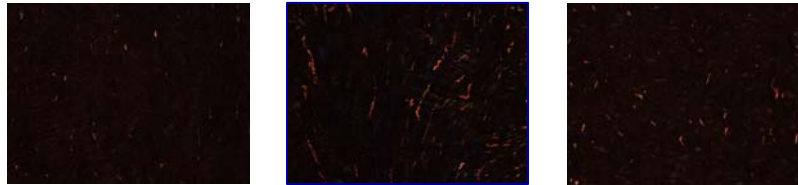


PETN post MI

- LV systolic and diastolic volume -

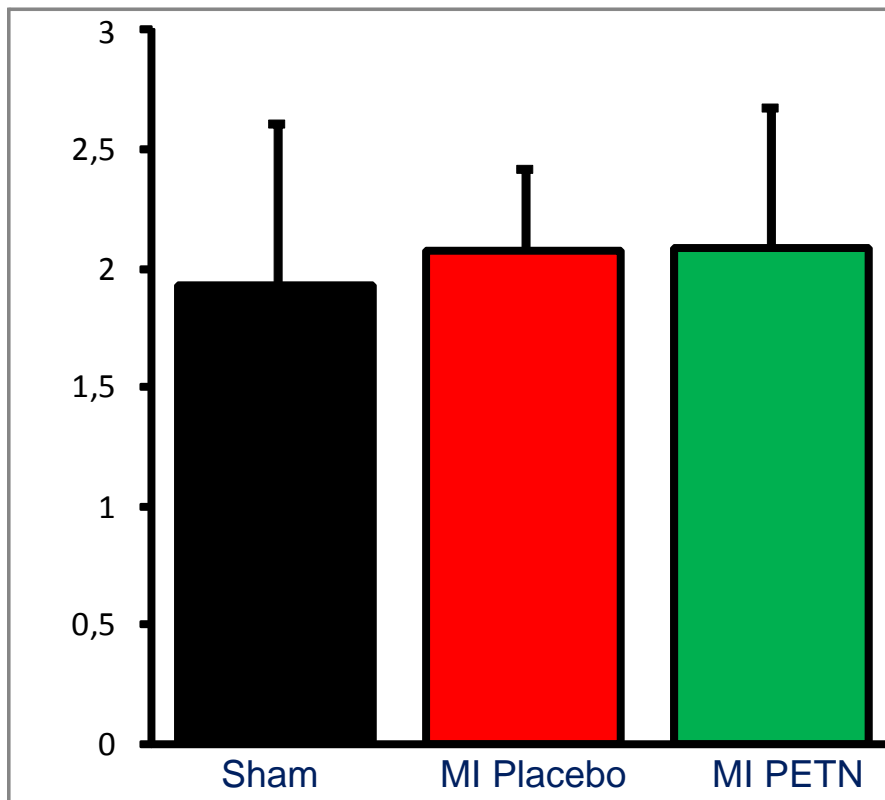


PETN post MI - collagen -

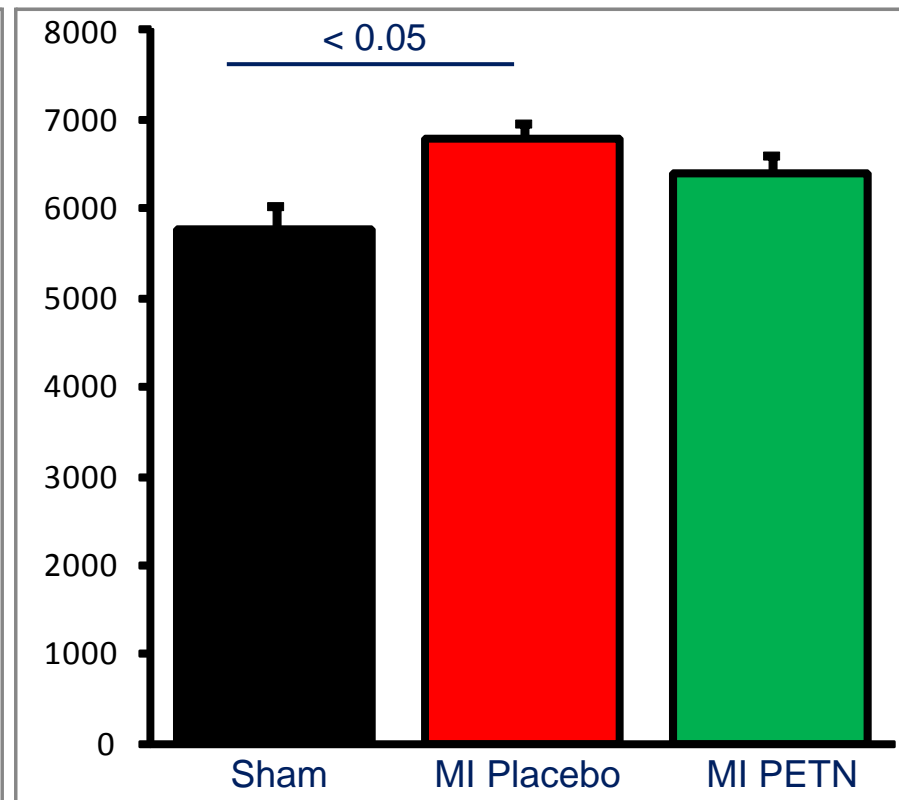


PETN post MI - cardiac hypertrophy-

LV/BW

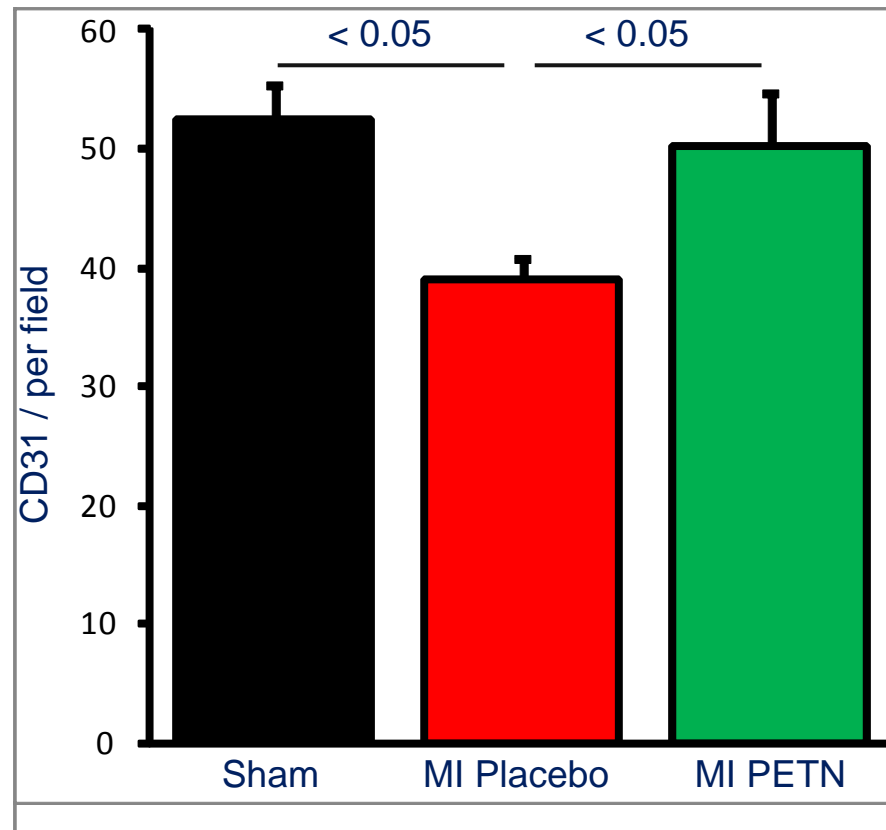


myocyte area

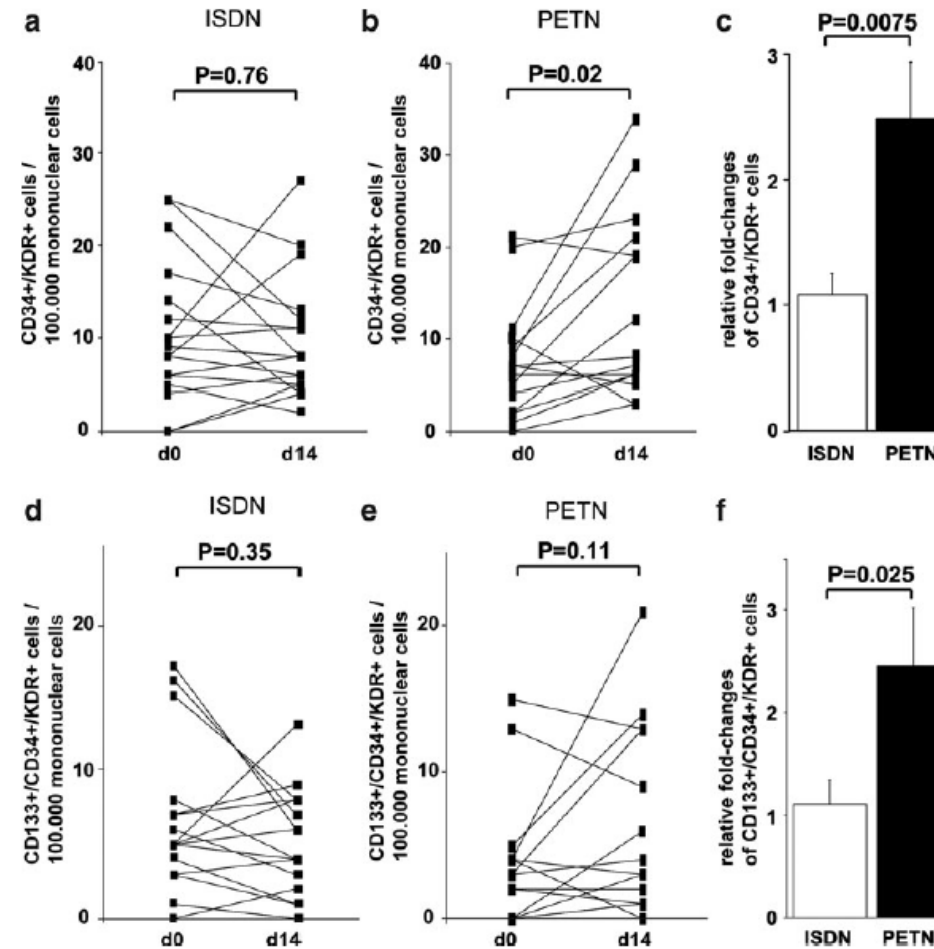


PETN post MI - angiogenesis-

CD 31-staining

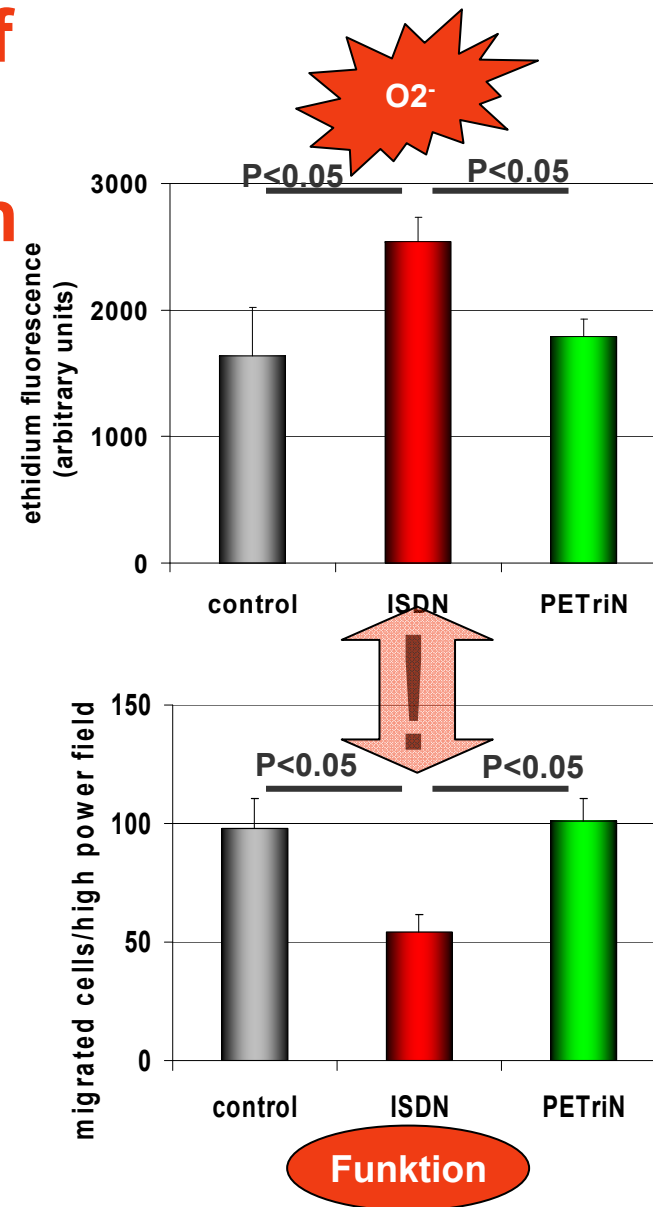
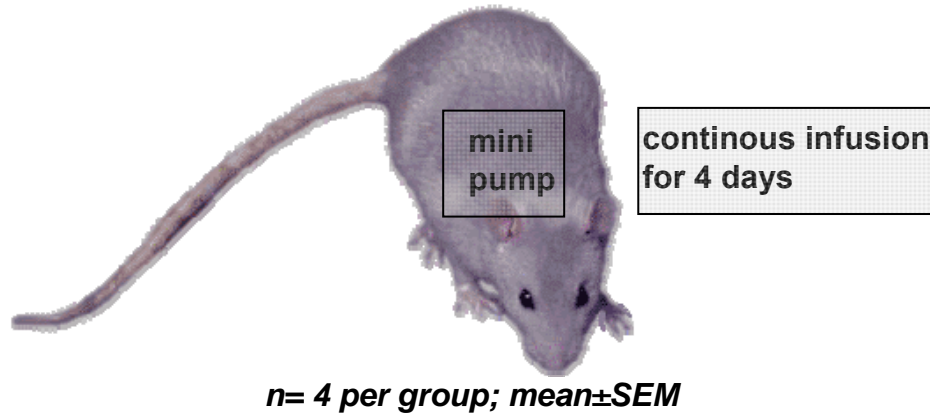


Effekte von PETN vs ISDN auf zirkulierende EPC-Spiegel bei Patienten mit KHK



Thum, Bauersachs,
Antioxid Redox Signal
2010

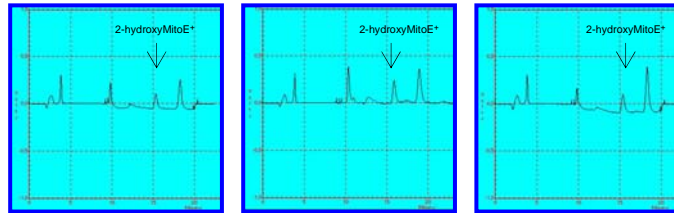
Effekte von Nitraten auf EPC-Funktion und Superoxid-Spiegel nach *in vivo* Behandlung



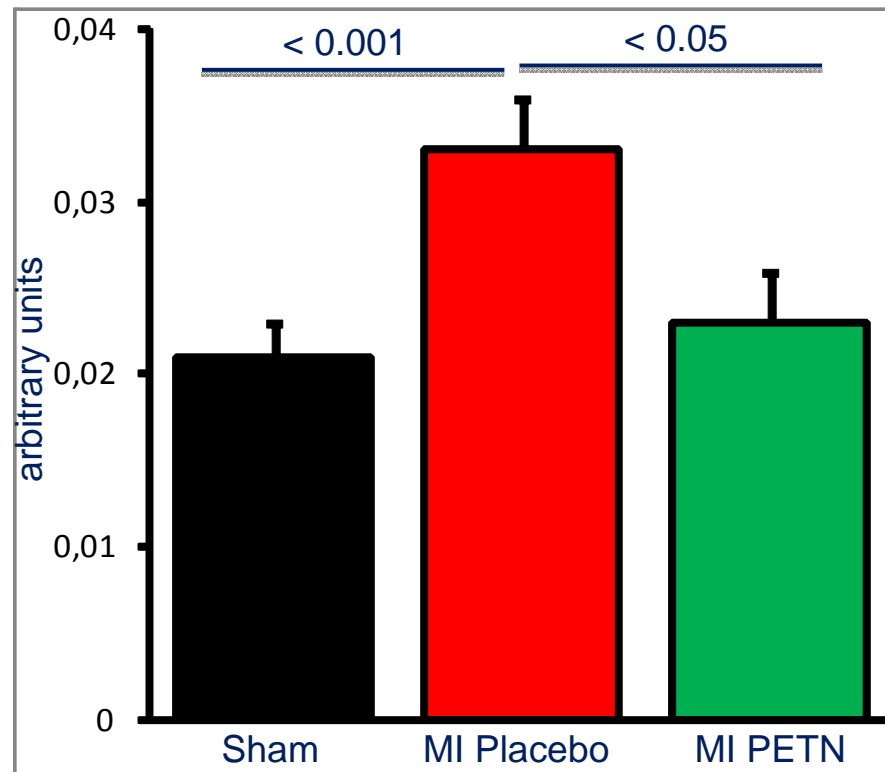
Thum, Bauersachs, ATVB 2007

PETN post MI

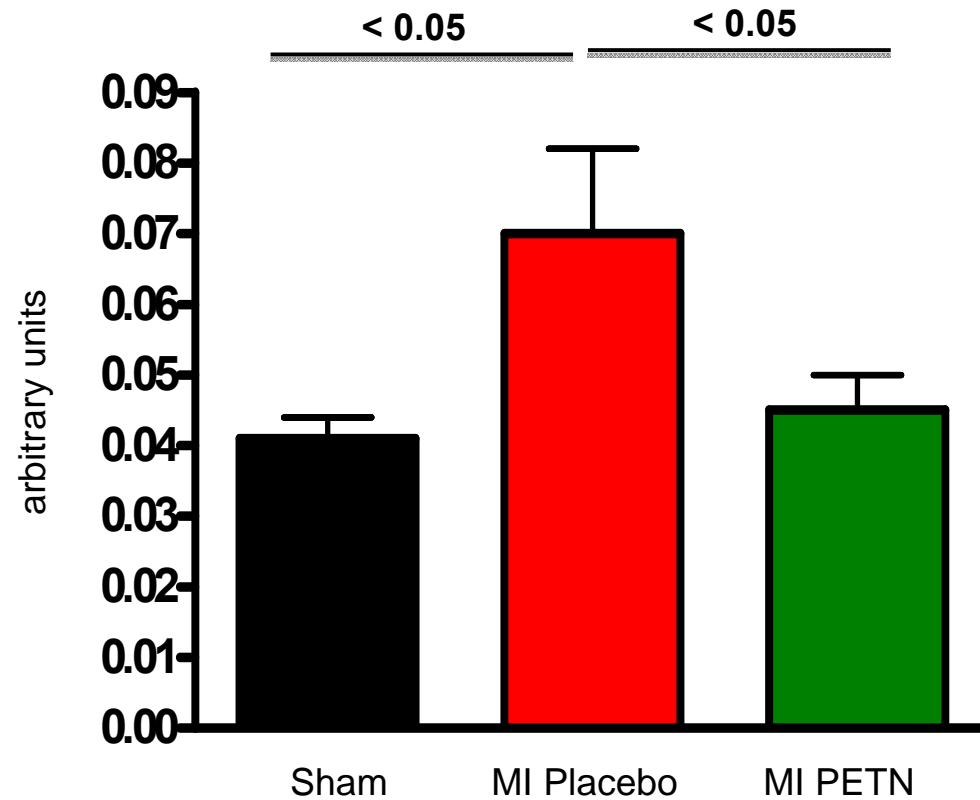
- mitochondrial ROS-production -



mitSOX-HPLC



PETN post MI: Oxidativer Stress in der Aorta



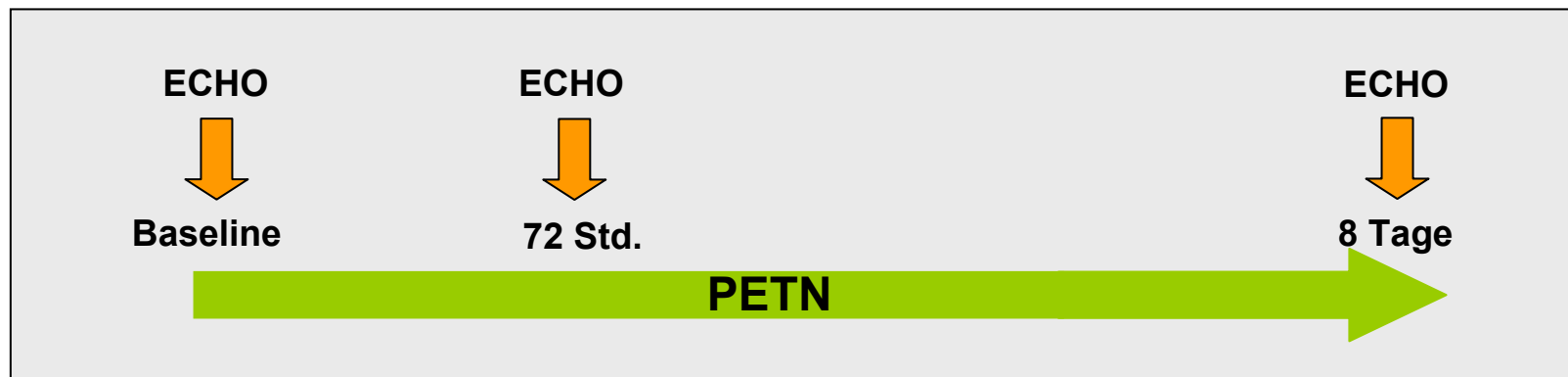
Zusammenfassung

Langzeit-Behandlung mit PETN nach experimentellem Myokardinfarkt

- verbessert kardiales Remodeling und Funktion
- vermindert oxidativen Stress in Herz und Gefäßen
- verbessert die myokardiale Angiogenese

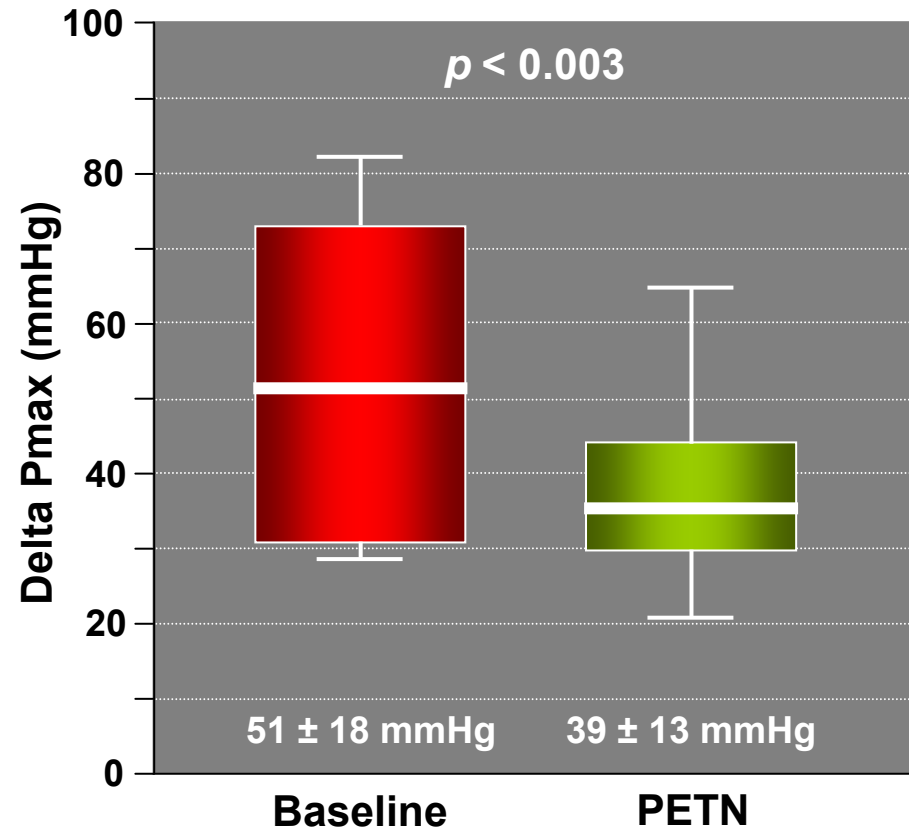
Pilotuntersuchung mit PETN bei chronischer Herzinsuffizienz mit pulmonaler Hypertonie

- Effekte von PETN bei 13 Patienten mit stabiler, symptomatischer Herzinsuffizienz (NYHA II / III) und pulmonaler Hypertonie
- Diagnose der pulmonalen Hypertonie mittels Echokardiographie
Def. PH: $V_{max} > 2,5$ m/s (PRVsyst > 25 mmHg)
- PETN (Pentalong[®]) 2 x 50 mg / Tag
Mittlere Therapiedauer: 6 Tage (akute / chronische Therapie)



Schneider CA, Erdmann E. In: Mutschler E, Erdmann E, Stalleiken D (Hrsg.):
Pentaerithryltetranitrat – Vasoselektivität und therapeutische Perspektiven

Pilotuntersuchung mit PETN bei chronischer Herzinsuffizienz mit pulmonaler Hypertonie



Schneider CA, Erdmann E. In: Mutschler E, Erdmann E, Stalleiken D (Hrsg.):
Pentaerithryltetranitrat – Vasoselektivität und therapeutische Perspektiven

CAESAR-Studie

„ClinicAI Efficacy Study of Pentalong for PulmonAry Hypertension in HeaRt Failure“

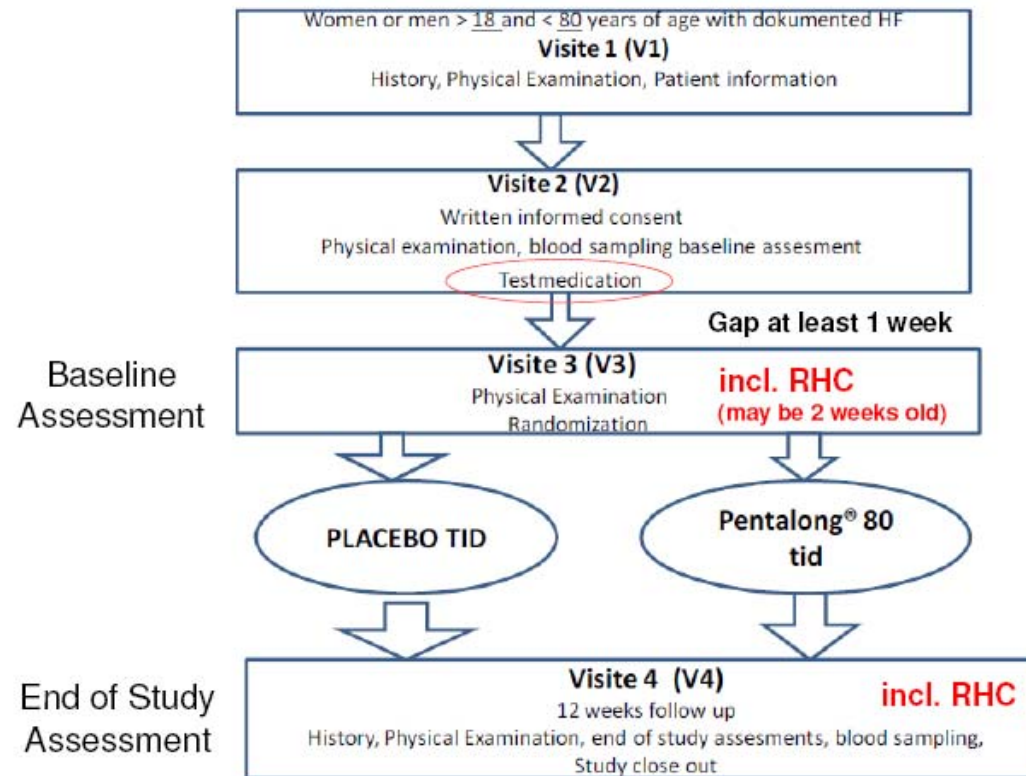
Primary objective :

The primary objective of this trial is to show superiority of PETN over Placebo of a 12 week oral Pentalong® long-term HF medication on PVR in patients suffering from HF

Secondary objectives:

safety and tolerability of Pentalong® therapy; exercise capacity (6MWD); echocardiographic variables (PAPsyst, LVEF, FS, TAPSE); right heart catheter variables (PCWP, PAPs, PAPd, PAPm, RAP, RVSP, RVEDP); quality of life (QOL-Questionnaire MLHFQ); biomarkers (NTproBNP, optional: CT-proET-1, MR-proADM, Troponin-I)

CAESAR-Studie Flow Chart



Dank an

D. Fraccarollo

J. Neuser

P. Galuppo

A. Schäfer

T. Thum

J. Widder

