*5th Lugano Stem Cell Meeting*
*Università della Svizzera Italiana, Lugano, 20th-21st June 2016*

# Molecular mechanisms of age-related endothelial dysfunction and CVD

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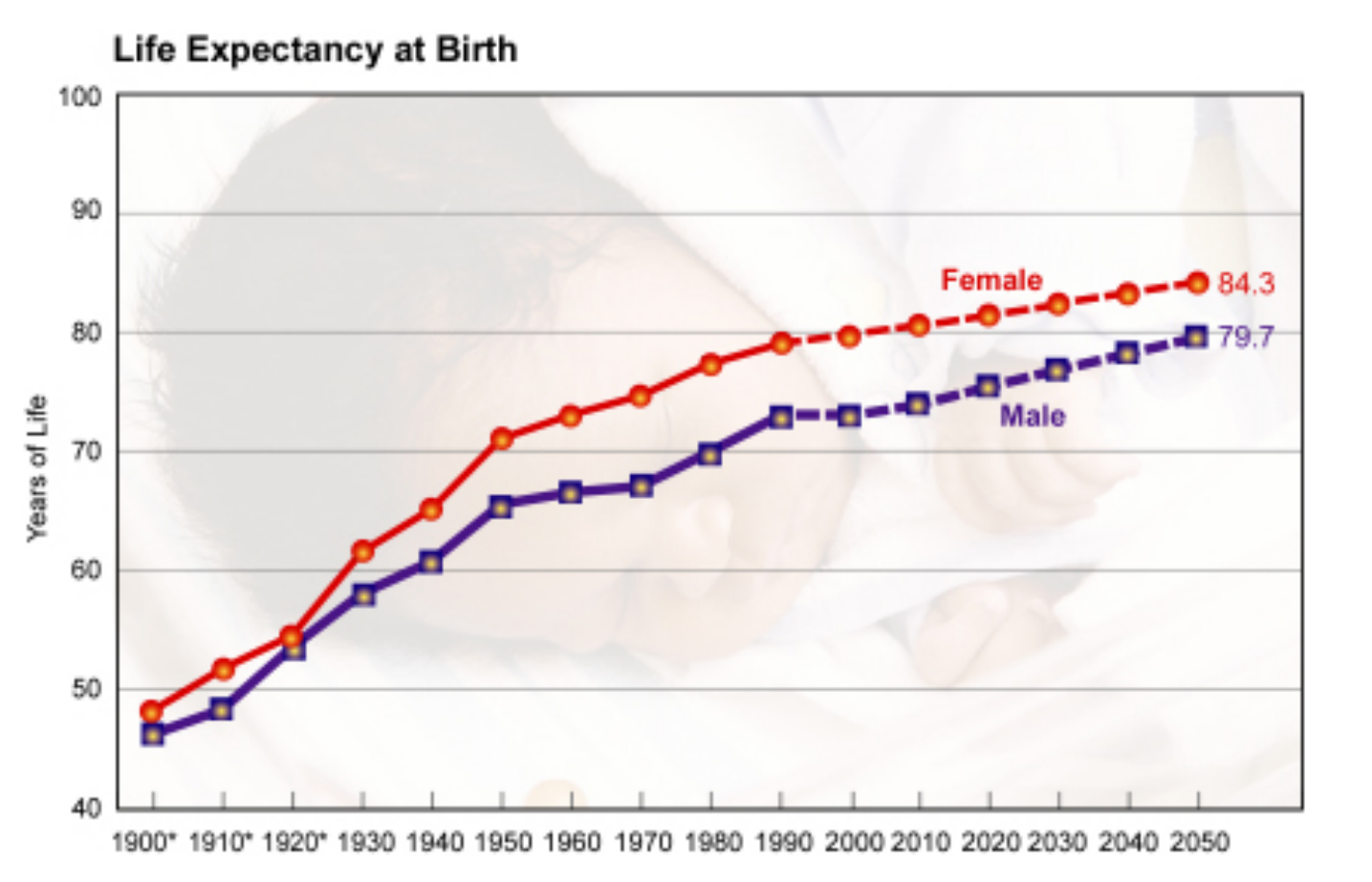
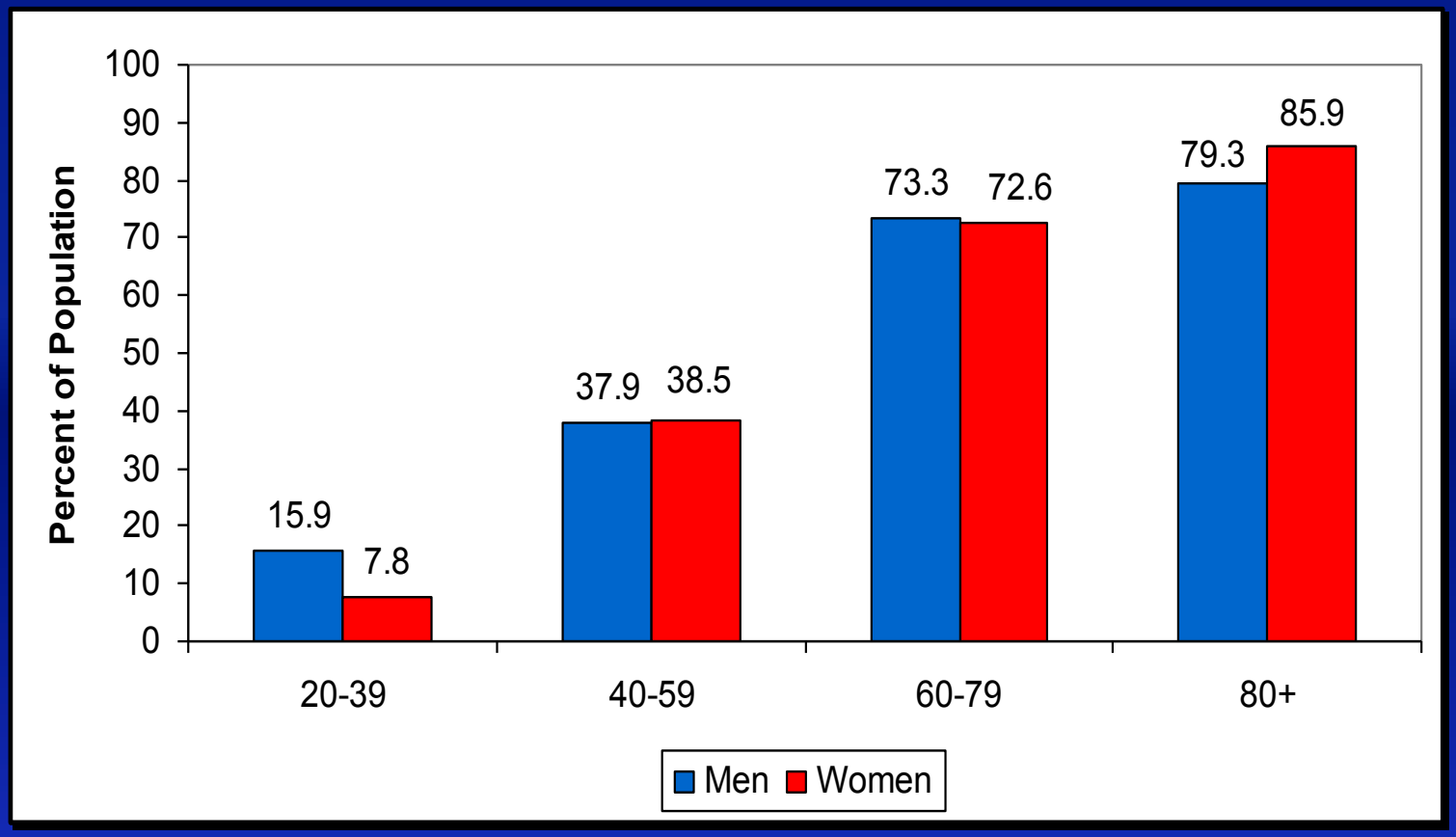
UniversitätsSpital Zürich

# Increasing Life Expectancy and Constant Birth Rates: Aging Pandemic?



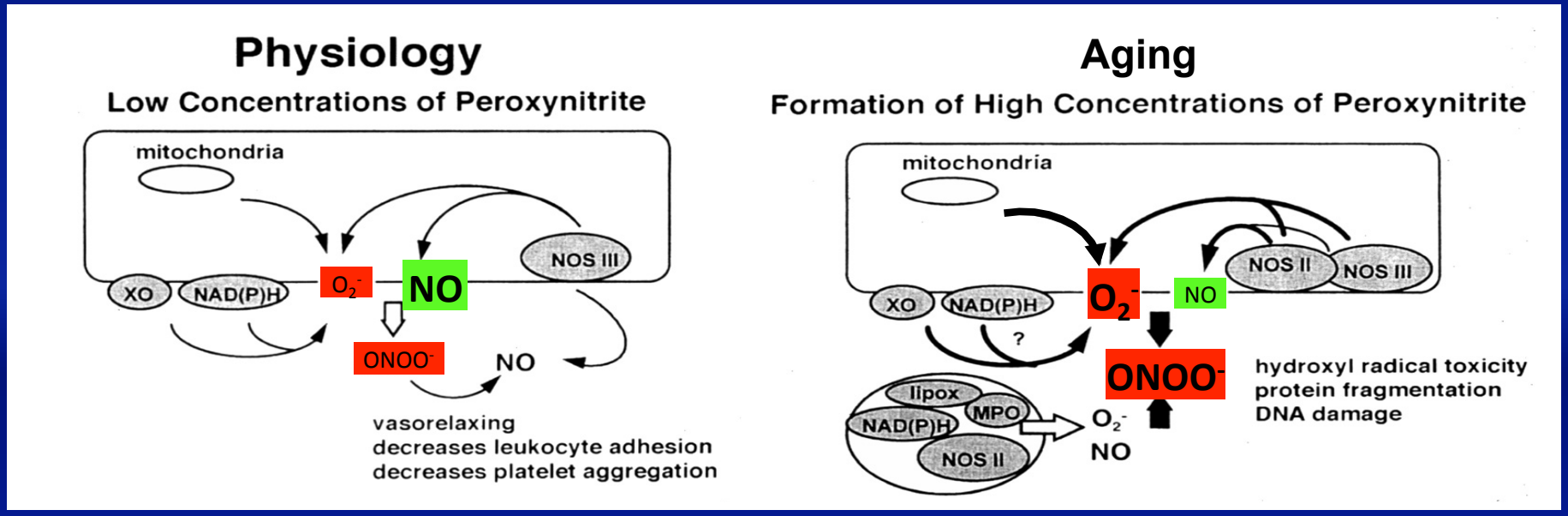

*"According to recent estimates by the Swiss Federal Statistics Office, approximately 10% more people aged over 80 will be alive in 2050 than today"*

# Prevalence of CVD/CBVD According to Age and Gender




*Roger et al., Circulation 2012*
*Cherubini A, et al., FAC, 2001*
*(NHANES: 2012). Source: NCHS and NHLBI.*

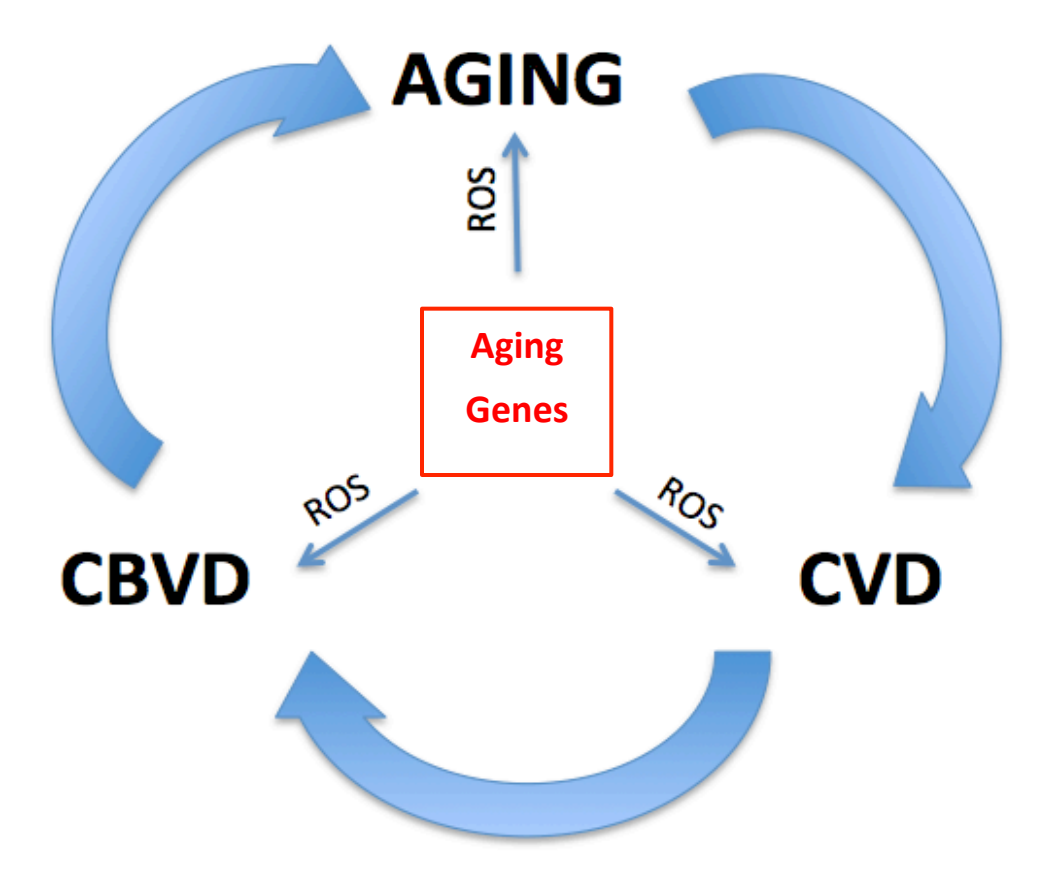
# Aging of the Vascular Endothelium



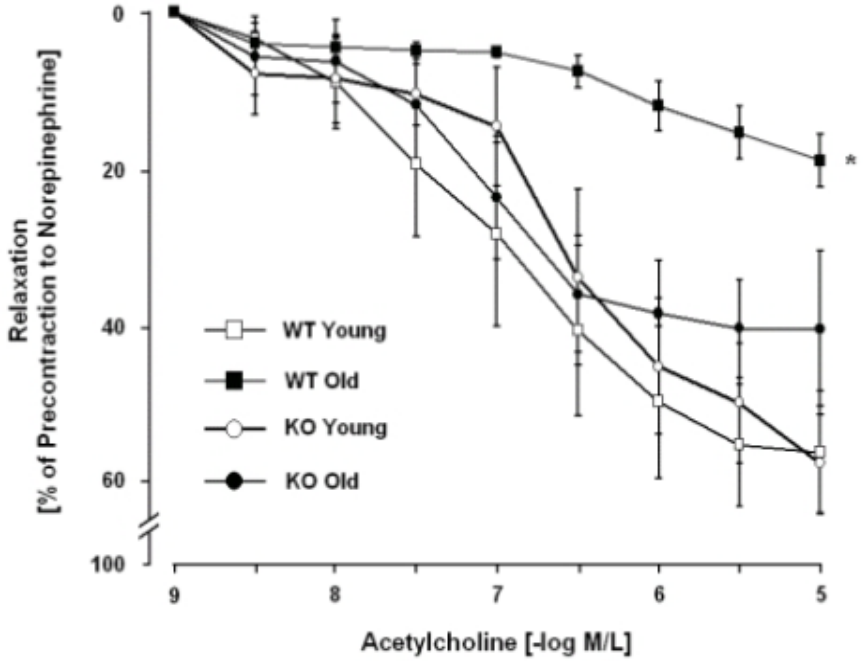

- High levels of protective NO
- Low levels of free radicals

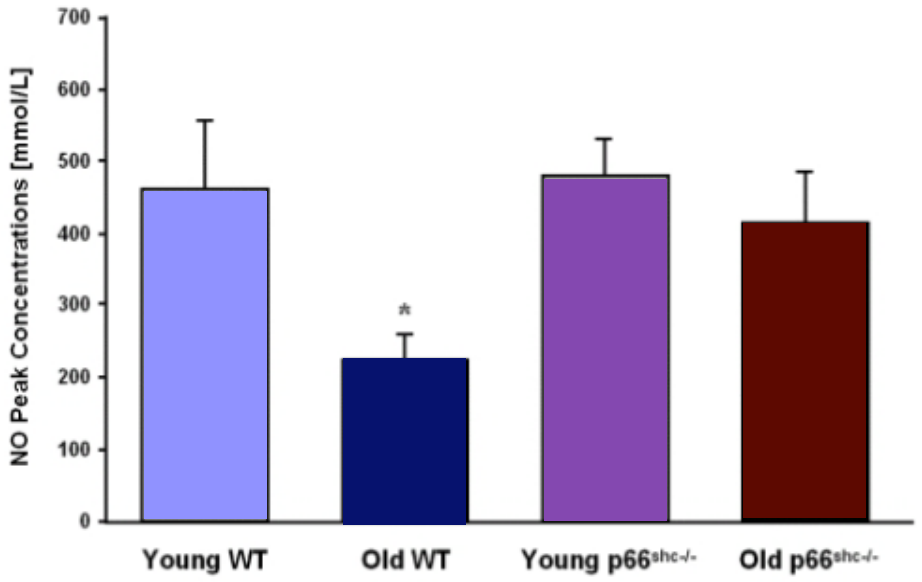
- Low levels of protective NO
- High levels of free radicals

# Working Hypothesis: Role of Aging Genes in Aging and Age-Dependent CVD & CBVD



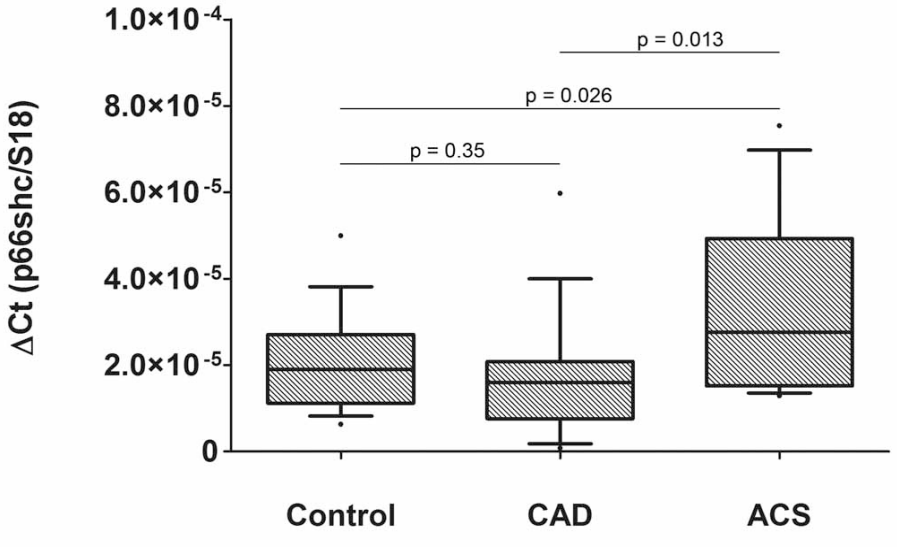
# The Aging p66Shc Mediates Age-Dependent ED via Increased ROS Production

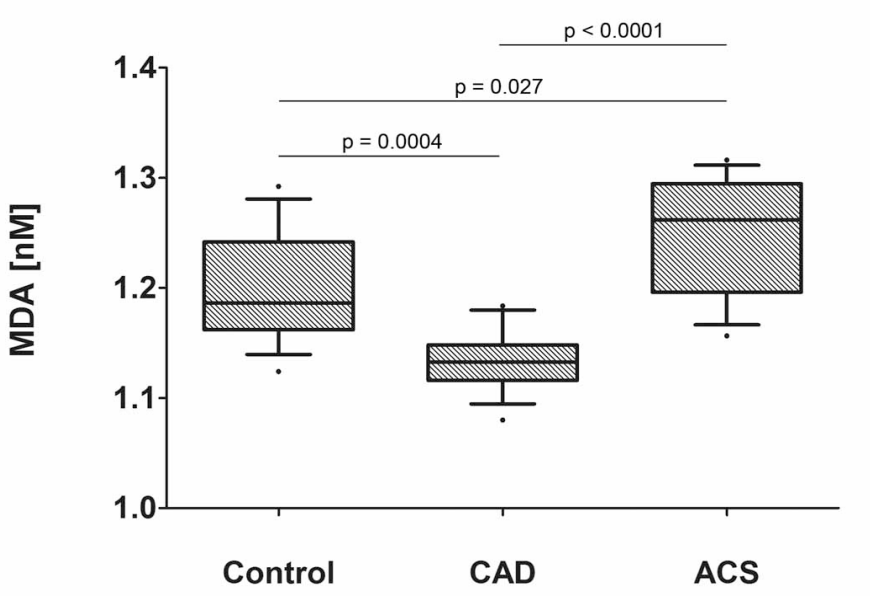



*Francia et al. Circulation 2004*

# P66 Shc Expression Patterns in Patients: Clinical Data



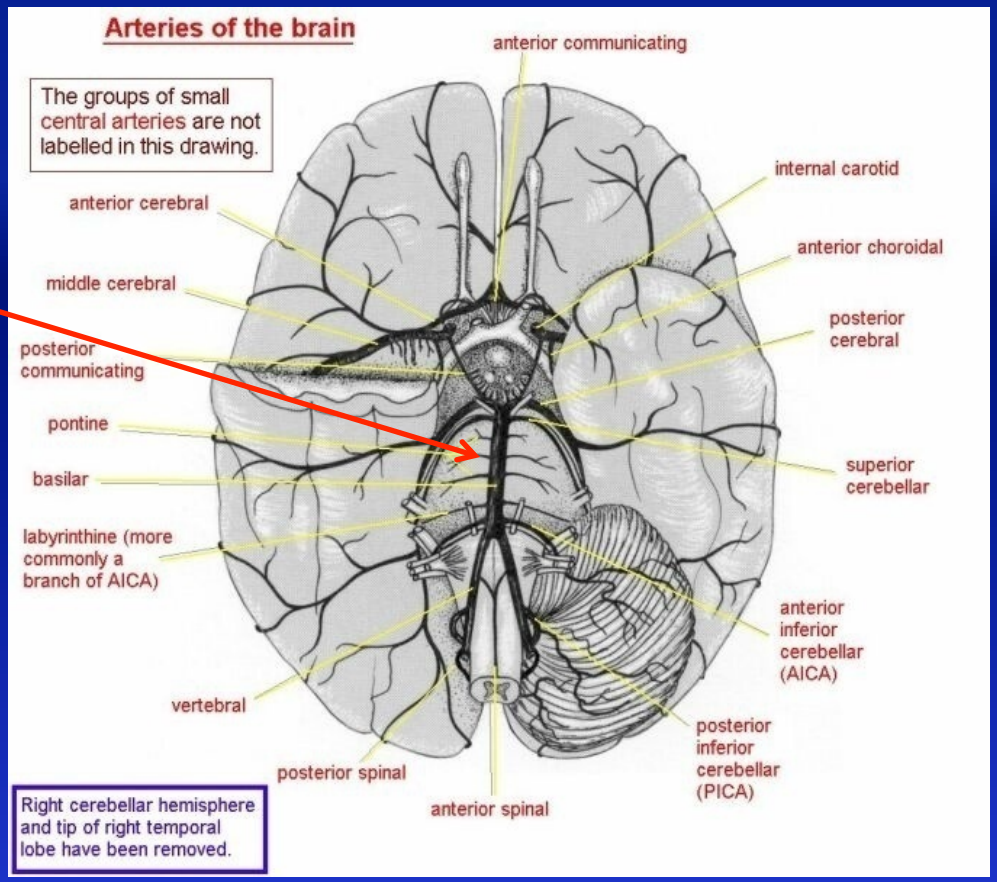

*Franzeck FC, et al, Atherosclerosis, 2012*

# Functional Studies of Cerebral Arteries

## Systemic vs cerebral arteries pathogenesis of aging

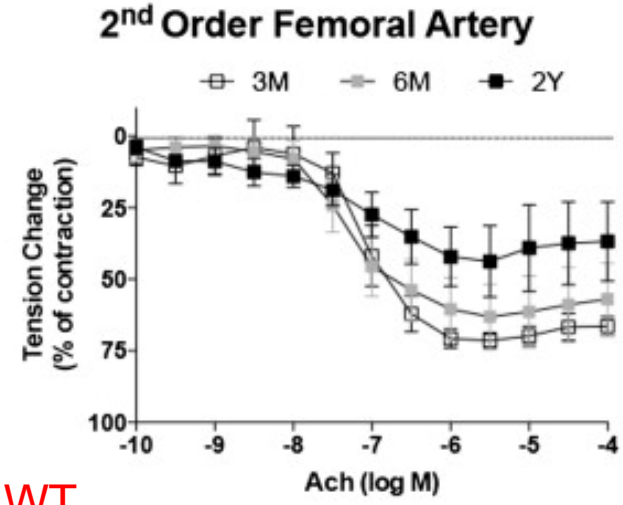
Cerebral arteries have higher NADPH Oxidase activity compared to systemic arteries

Functional studies

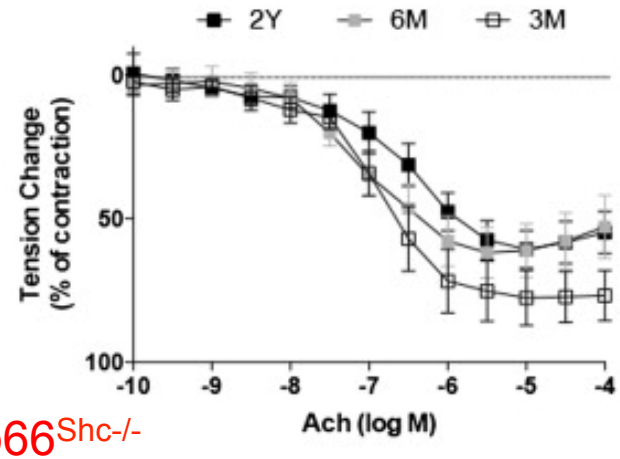



*Miller AA. Et al., Circ. Res. 2005*

# Systemic vs Cerebral arteries Pathogenesis of Aging



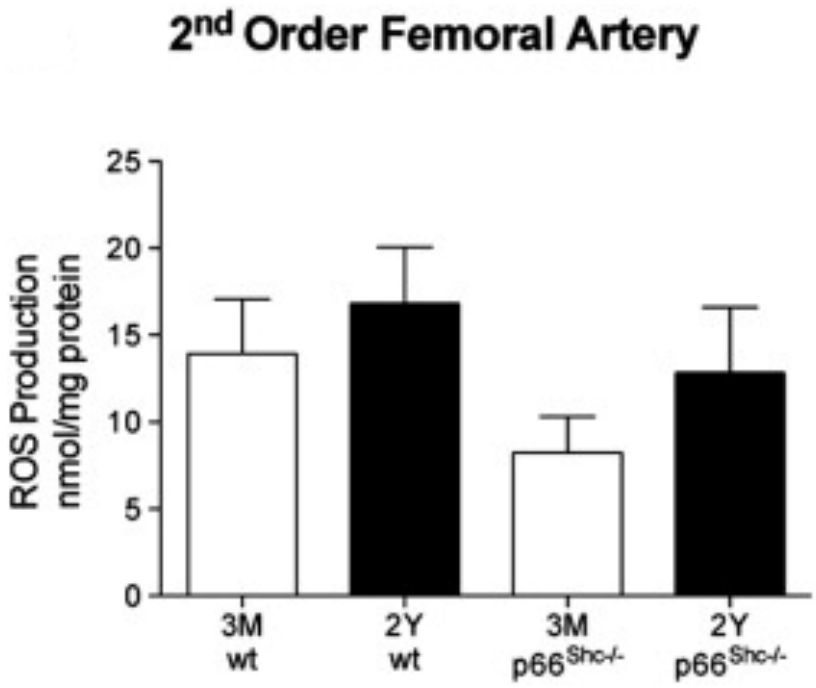

WT

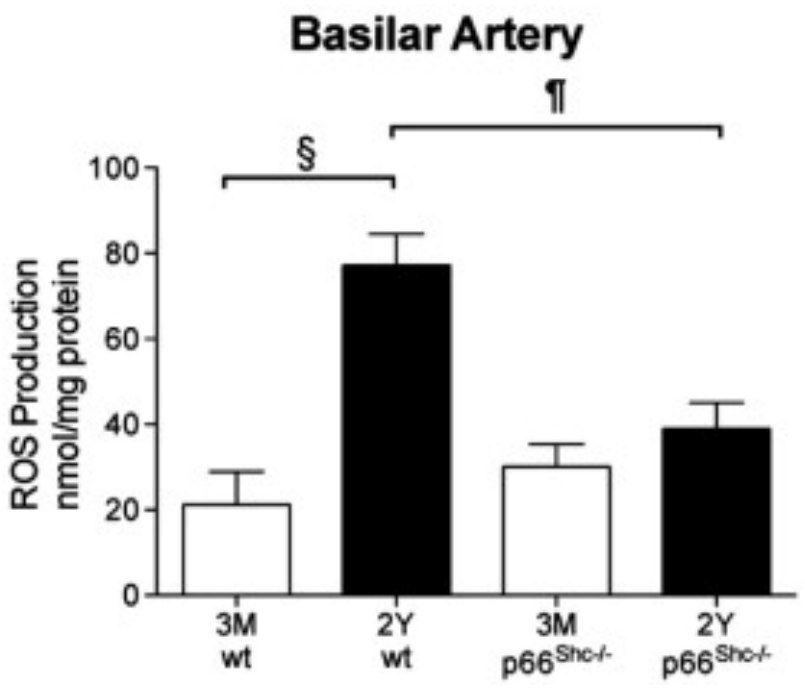



p66Shc-/-

*Shi Y and Savarese G, et al Int J Cardiol. 2014*

# Systemic vs Cerebral arteries Pathogenesis of Aging




*Shi Y and Savarese G, et al Int J Cardiol. 2014*

# Post-Ischemic p66$^{Shc}$ Silencing by siRNA

Ischemia
45 min

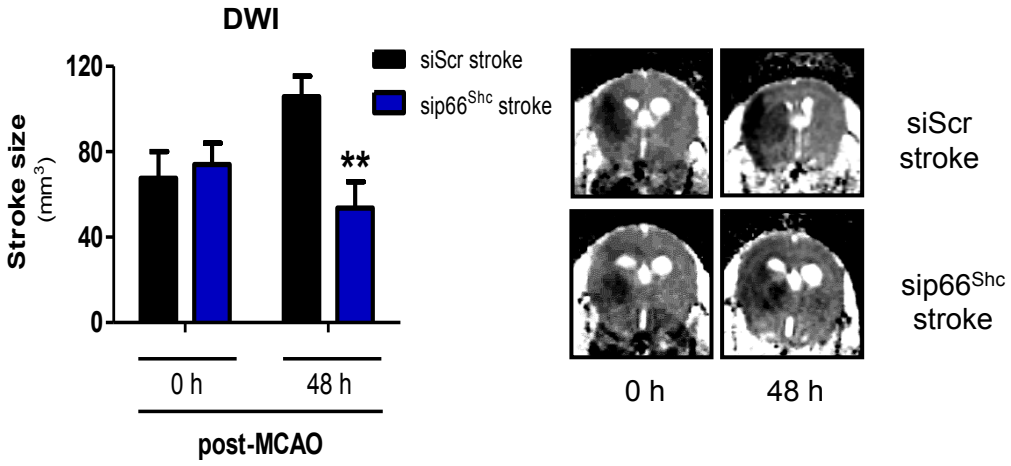
Reperfusion
48 h

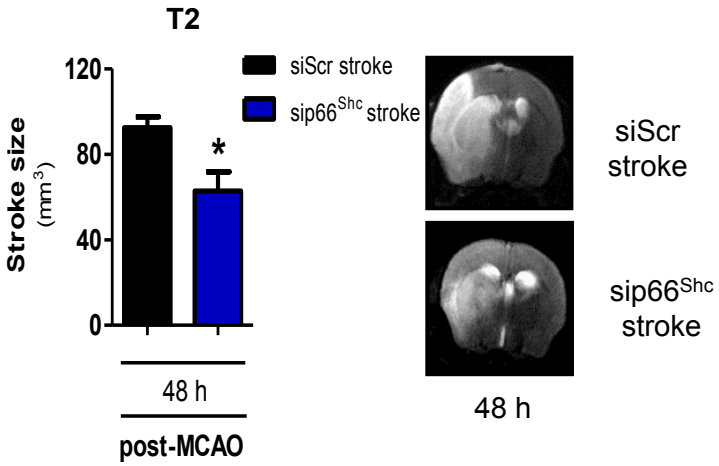
**MCAO**

- **Stroke Size**
- **Neurological Function**
- **BBB Permeability**
- **Survival Time**

**i.v. injection of p66$^{shc}$ siRNA**

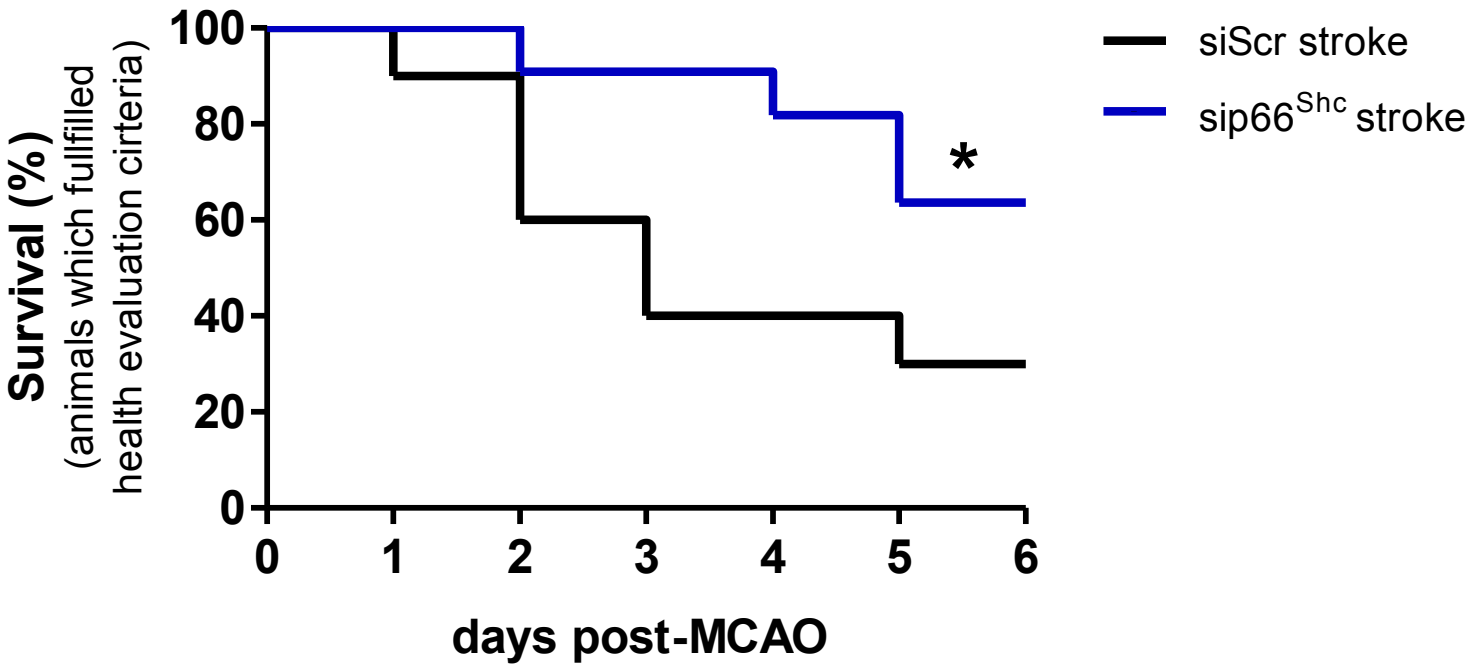
# Reduced Stroke Size in p66$^{Shc}$ Silenced Mice as Compared to Scrambled siRNA Injected Mice



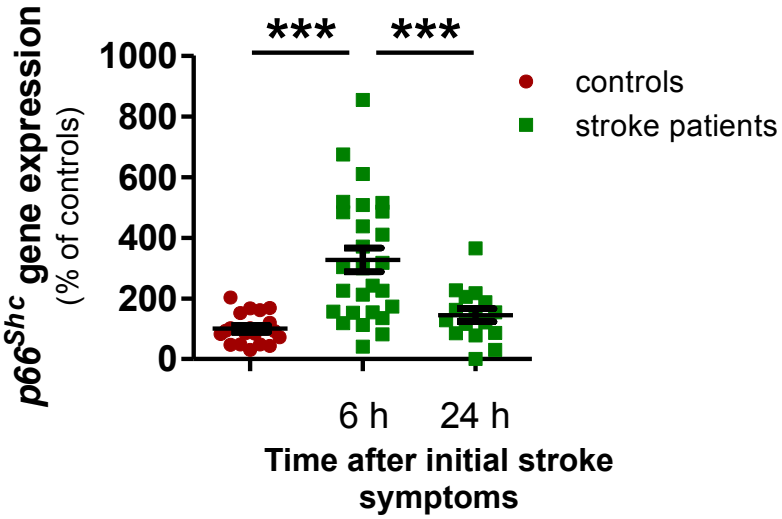

*Spescha RD, et al Eur Heart J. 2015 Jul 1;36(25)*

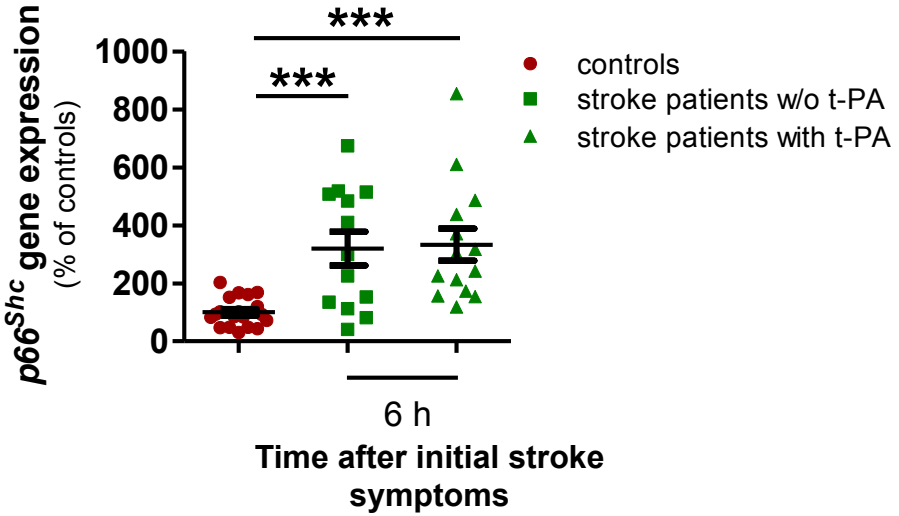
# Post-Ischemic *In Vivo* p66$^{Shc}$ Silencing Improves Survival Time after Stroke

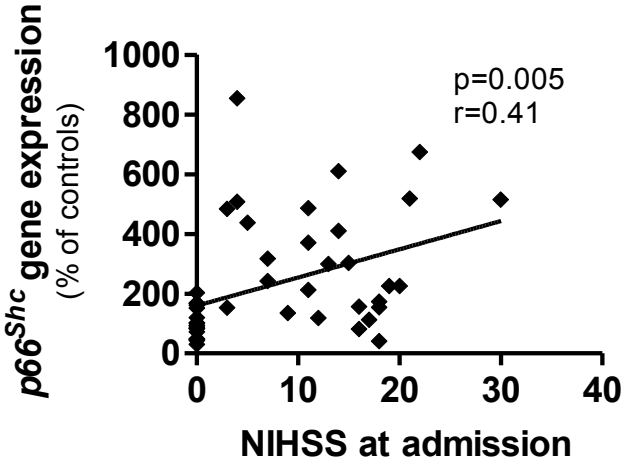


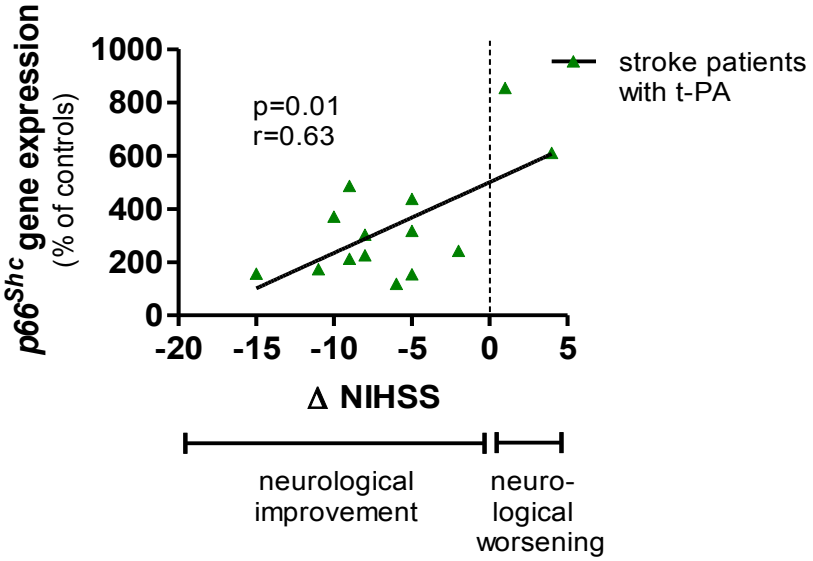

*Spescha RD, et al Eur Heart J. 2015 Jul 1;36(25)*

# p66 Shc Expression in PBM of Stroke Patients




*Spescha RD, et al Eur Heart J. 2015 Jul 1;36(25)*

# Conclusions

Genes controlling aging also mediate age-dependent vascular dysfunction and age-dependent CVD and CBVD

A common denominator between aging and age-dependent CVD and CBVD is increased production of free radicals

Further characterisation of the molecular mechanisms of aging will be key in discovering novel therapeutical targets for the treatment of age-dependent CVD and CBVD

ZIHP

ZURICH HEART HOUSE
foundation for cardiovascular research

ZNZ Zentrum für Neurowissenschaften Zürich
Neuroscience Center Zurich

# THANK YOU !

**Grants for translational and clinical cardiac and oncological research**

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FONDS NATIONAL SUISSE
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Fondazione Svizzera di Cardiologia

NOVARTIS
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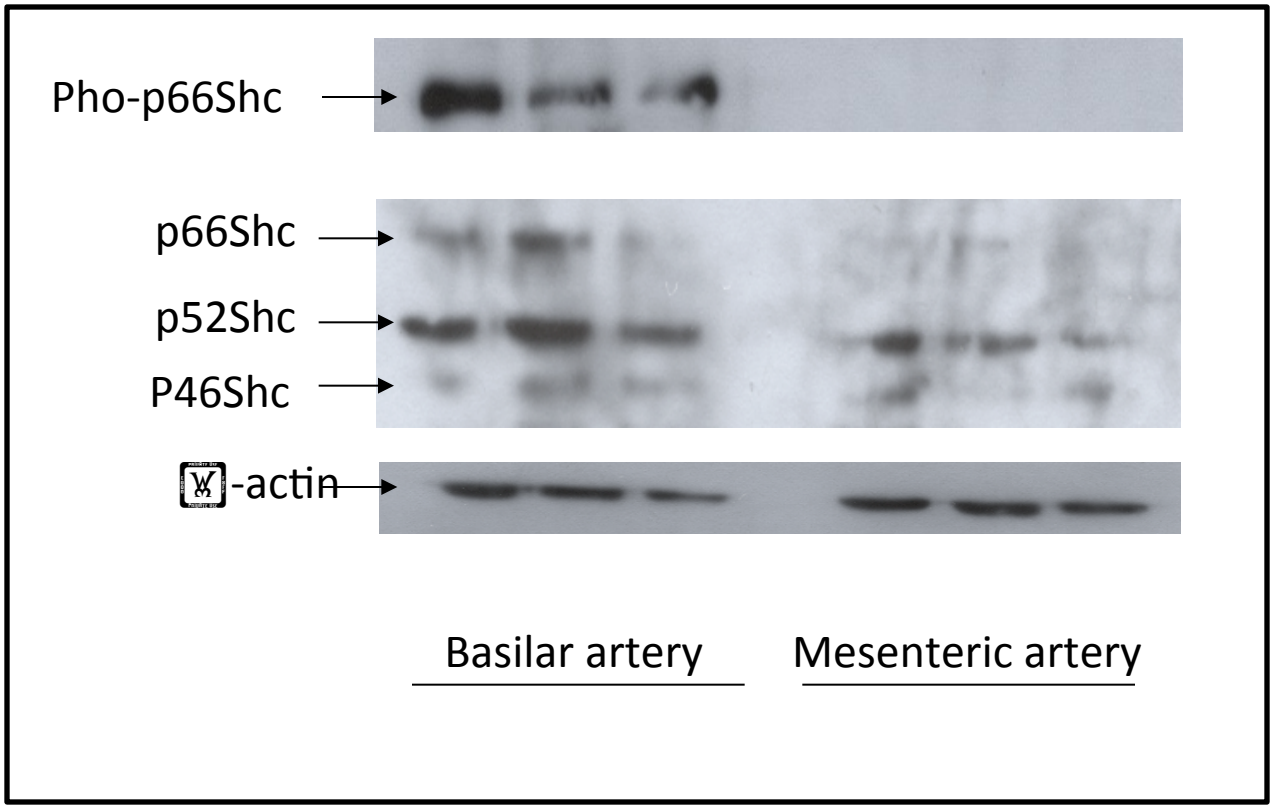
# Physiological Aspects of Vascular Aging

# Research Tools for Studying Aging

Studying aging in humans is difficult as this always occurs in tandem with other risk factors such as atherosclerosis

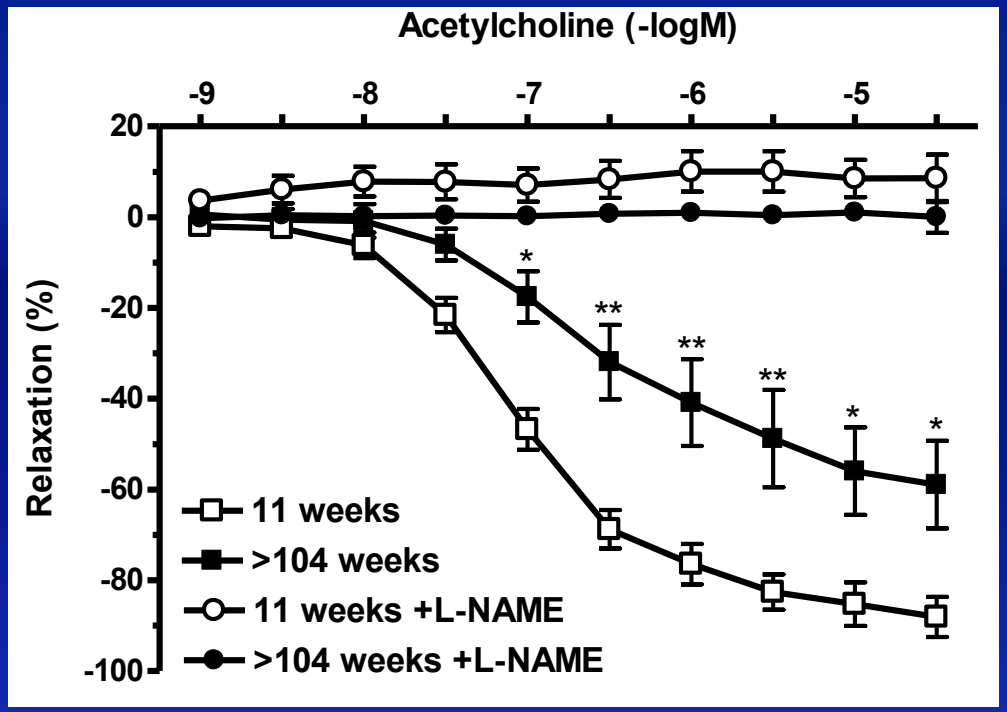
Mice offer an ideal system for studying aging as they do not spontaneously develop atherosclerosis

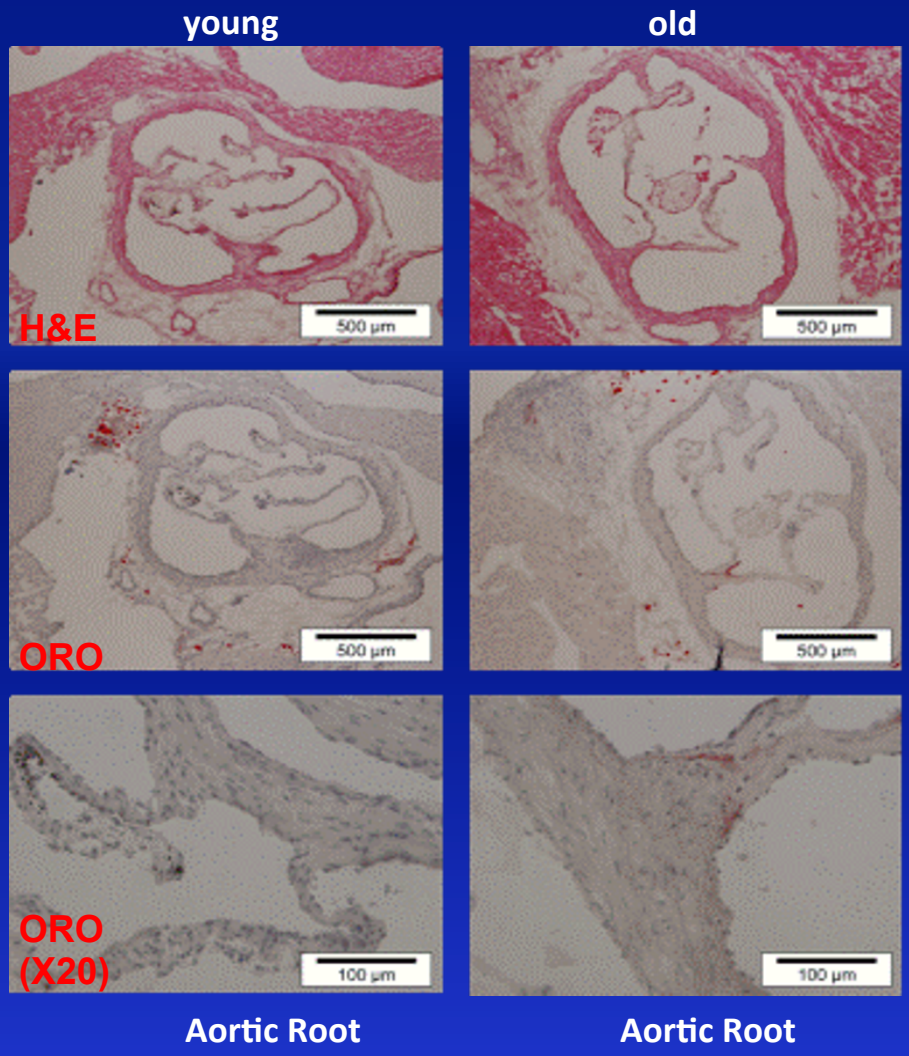
# Systemic vs Cerebral arteries Pathogenesis of Aging




*Unpublished data*

# Aging is an Independent Risk Factor for Vascular Dysfunction




*Stämpfli S, et. al. 2010 ATVB*

# Vascular Aging and the Free Radicals Theory

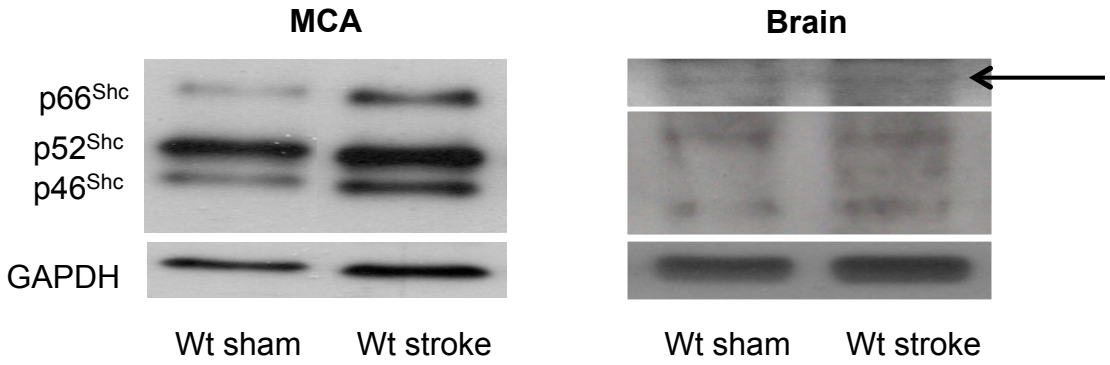
Vascular aging is characterised by the transition of the endothelium from an **anti-**atherosclerotic/thrombotic state to a **pro-**atherosclerotic/thrombotic one

The free radicals theory of aging was conceived by D. Harman in the 1950s and states that cells accumulate free radicals over time causing damage to enzymes and DNA

*Harman D, et al, J Gerontol. 1956*

# Genes and Molecular Mediators of Vascular Aging and Risk Factors

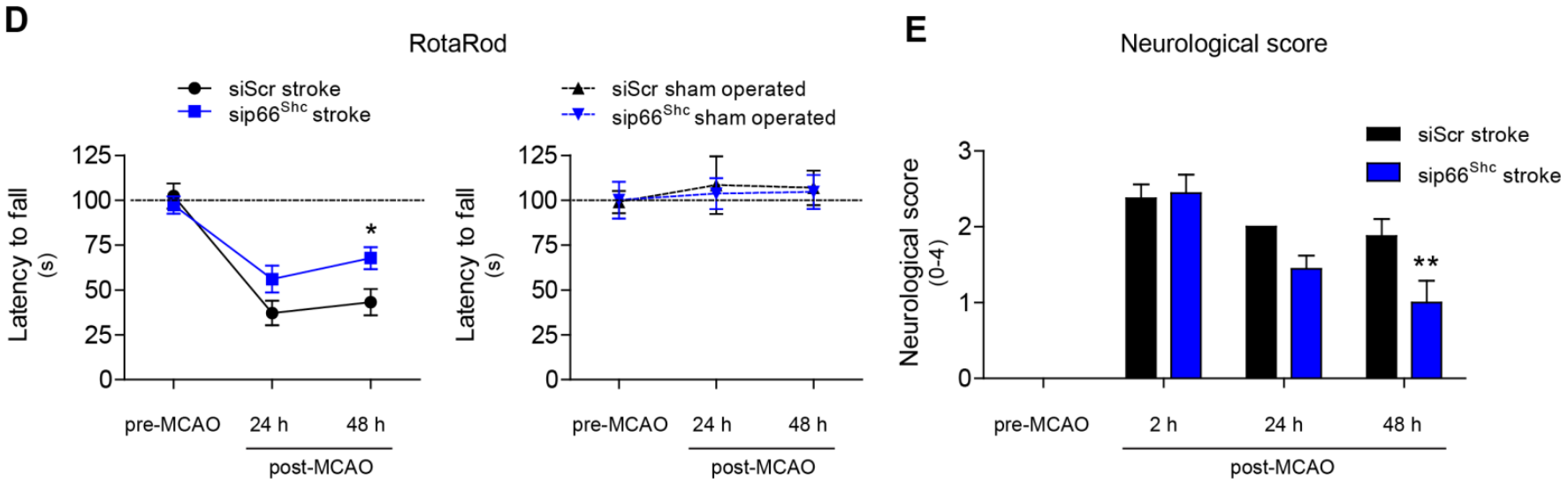
# Following I/R p66$^{Shc}$ Protein Is Increased in the MCA, but not in Whole Brain




→ Cerebrovascular p66$^{Shc}$ rather than neuronal p66$^{Shc}$ maybe an important mediator of ischemia/reperfusion brain injury

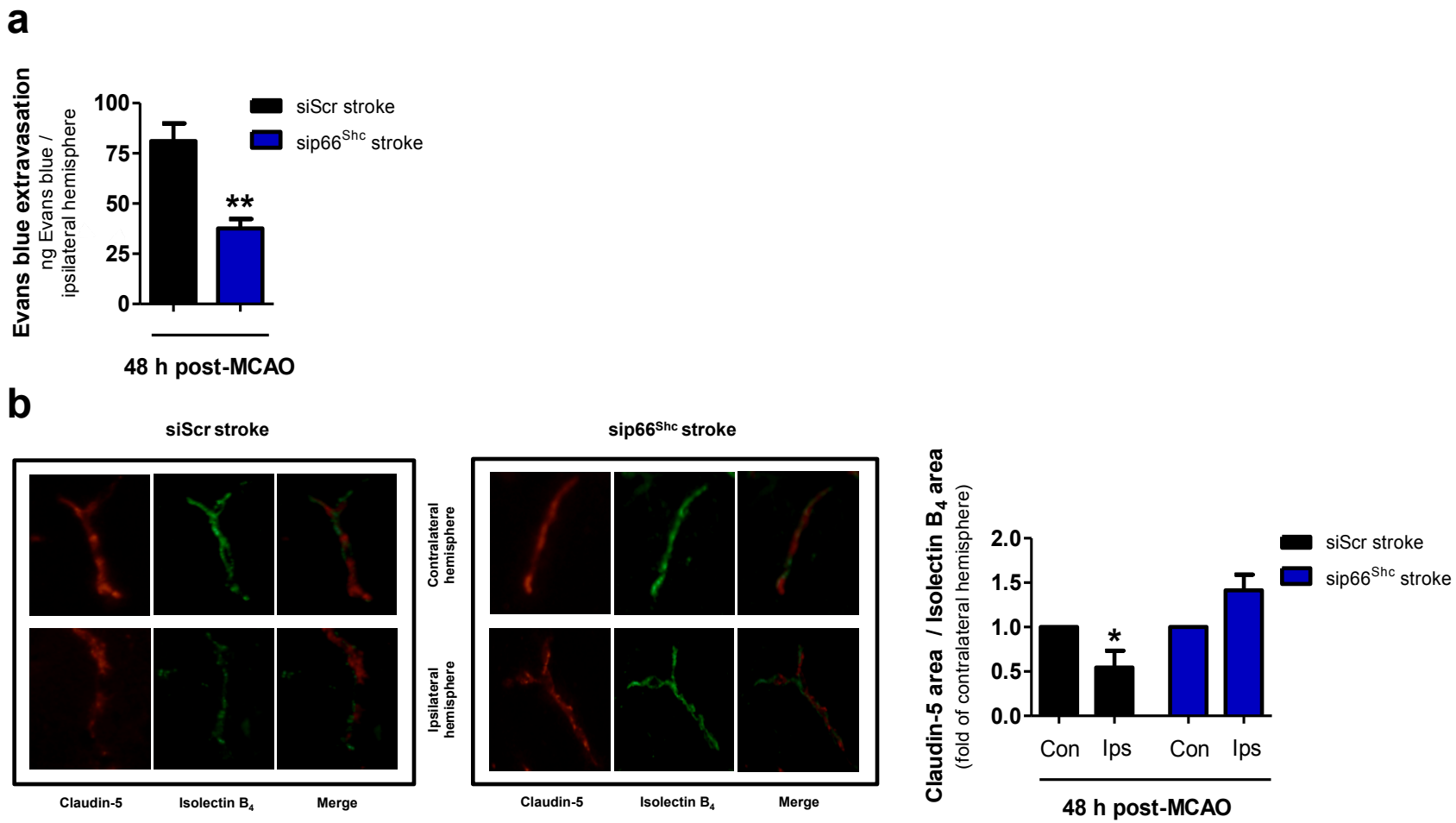
Spescha RD ,et al, *Eur Heart J*. 2013

# Post-Ischemic *In Vivo* p66$^{Shc}$ Silencing Reduces Neurological Deficits after Stroke



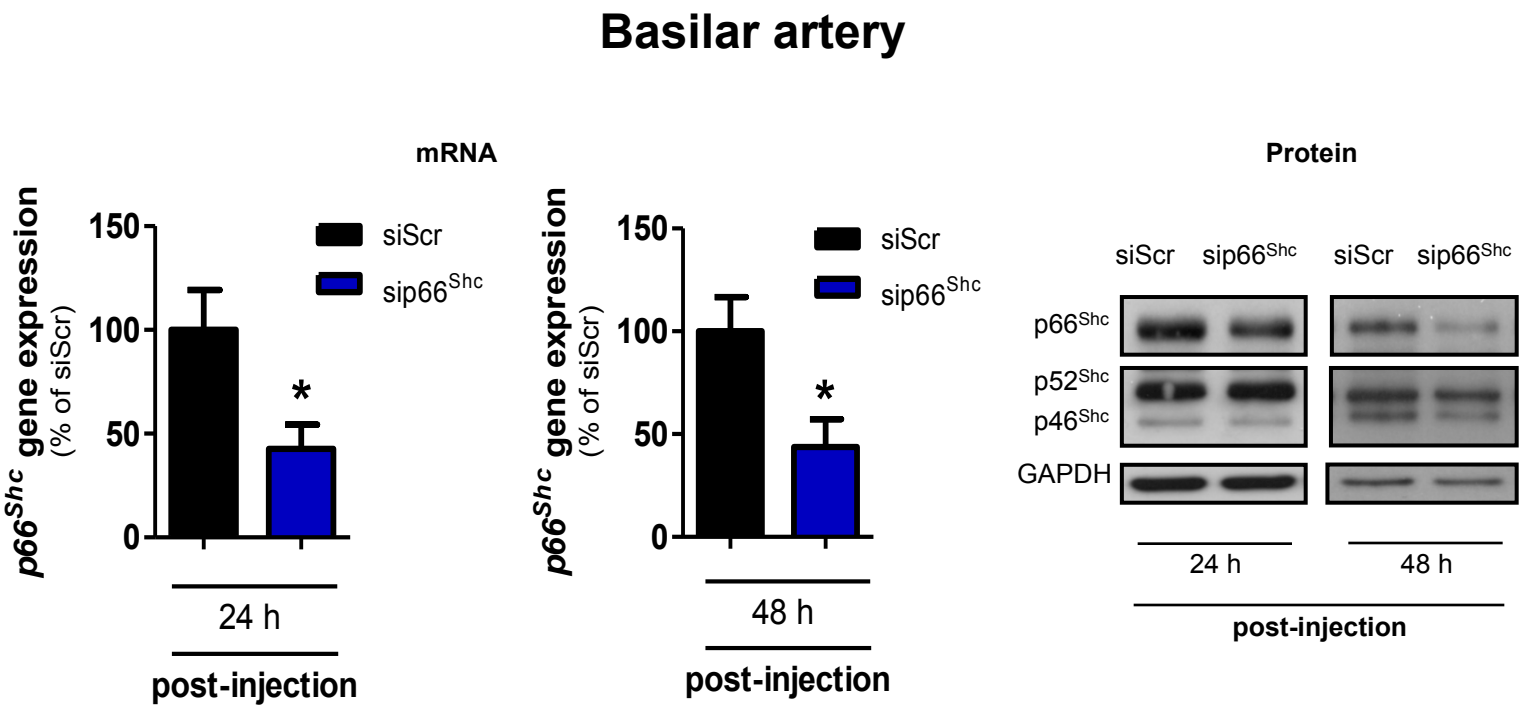

*Spescha RD, et al Eur Heart J. 2015 Jul 1;36(25)*

# Post-Ischemic *In Vivo* p66$^{Shc}$ Silencing Preserves BBB Integrity After Ischemia/Reperfusion



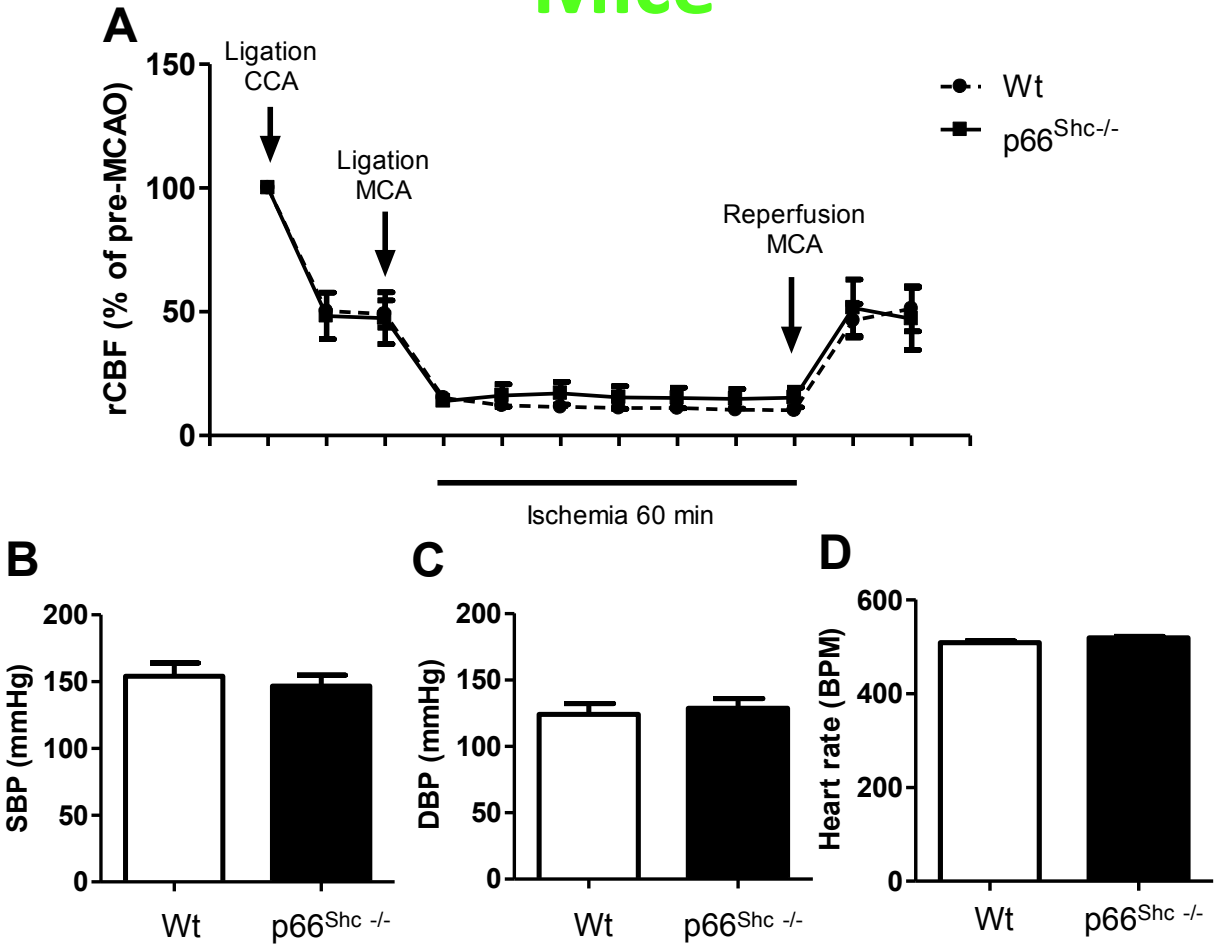

*Manuscript in press, Apr 2015*

# Post-Ischemic p66$^{Shc}$ Silencing by siRNA



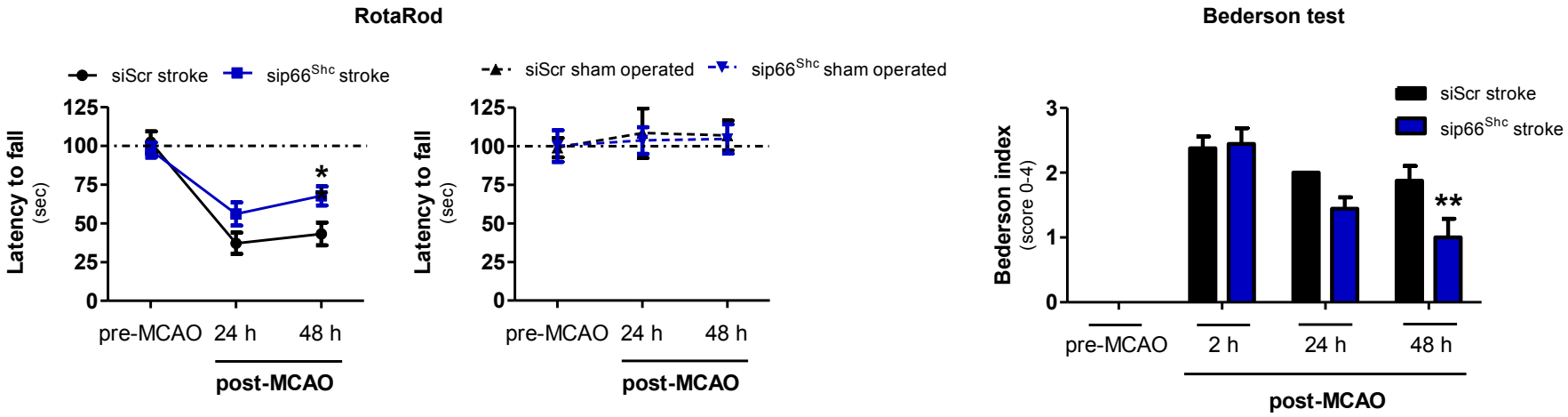

*Manuscript in press, Apr 2015*

# Comparable Cerebral Perfusion and Systemic Blood Pressure in Wt and p66$^{Shc-/-}$ Mice




Spescha RD ,et al, *Eur Heart J*. 2013

# Post-Ischemic *In Vivo* p66$^{Shc}$ Silencing Reduces Neurological Deficits after Stroke




*Unpublished data*