Physiologic ischemia training
a new approach in rehabilitation of ischemic heart disease

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Ischemia- the most common pathology in human diseases and injuries

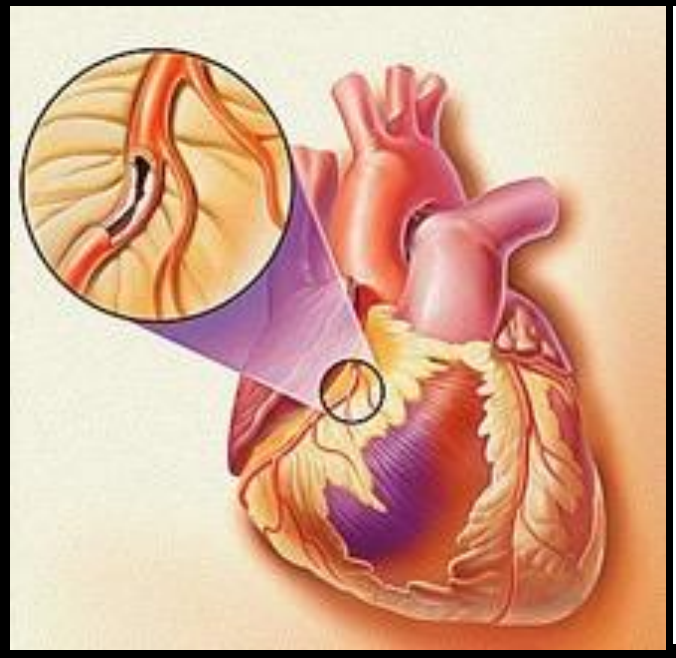
- Coronary artery disease
- Thrombosis
  - brain infarction
  - DVT
  - PTE
- Varies chronic diseases

Outcome of ischemia

- **Long and severe ischemia: tissue necrosis**
  - Brain infarction
  - Myocardia infarction
  - Limb infarction
- **Repeated short-time ischemia: collateral formation**
  - Red face at High Plateau
  - Cardiac collateral formation
  - Cerebral collateral formation

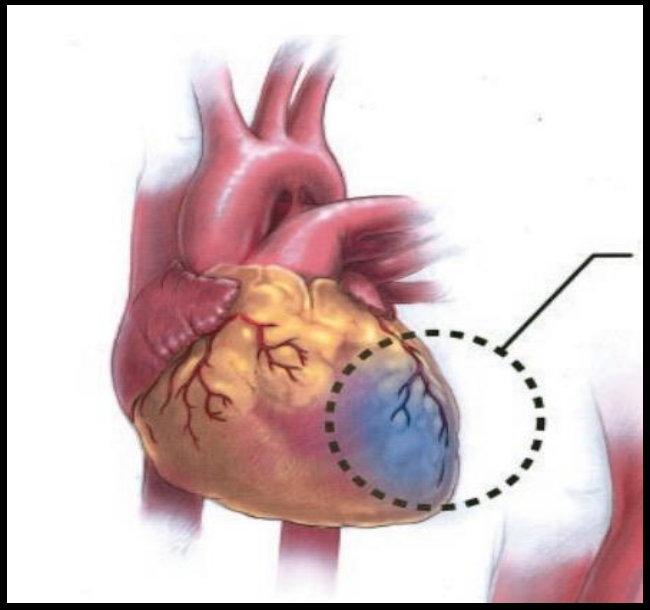
Coronary artery disease

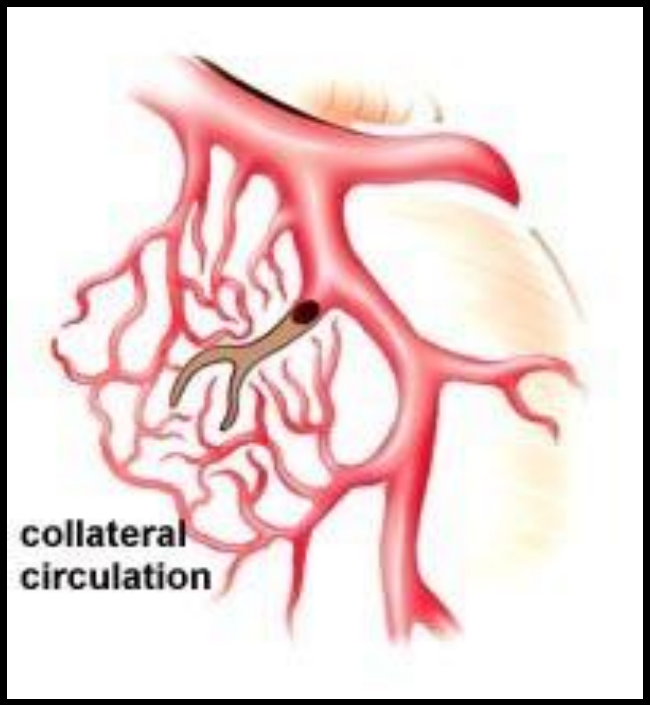
- **Pathophysiology:**
  - imbalance of myocardial blood supply and consumption
- **Clinical strategy:**
  - Reduce consumption
  - Increase supply



Collateral formation is important to increase supply

- Patients with repeated ischemia (angina or silent ischemia) may have
  - lesser opportunity of myocardial infarction
  - smaller size of myocardial infarction as well as fewer fatal infarction when heart attack happened.





Blood vascular collateral formation

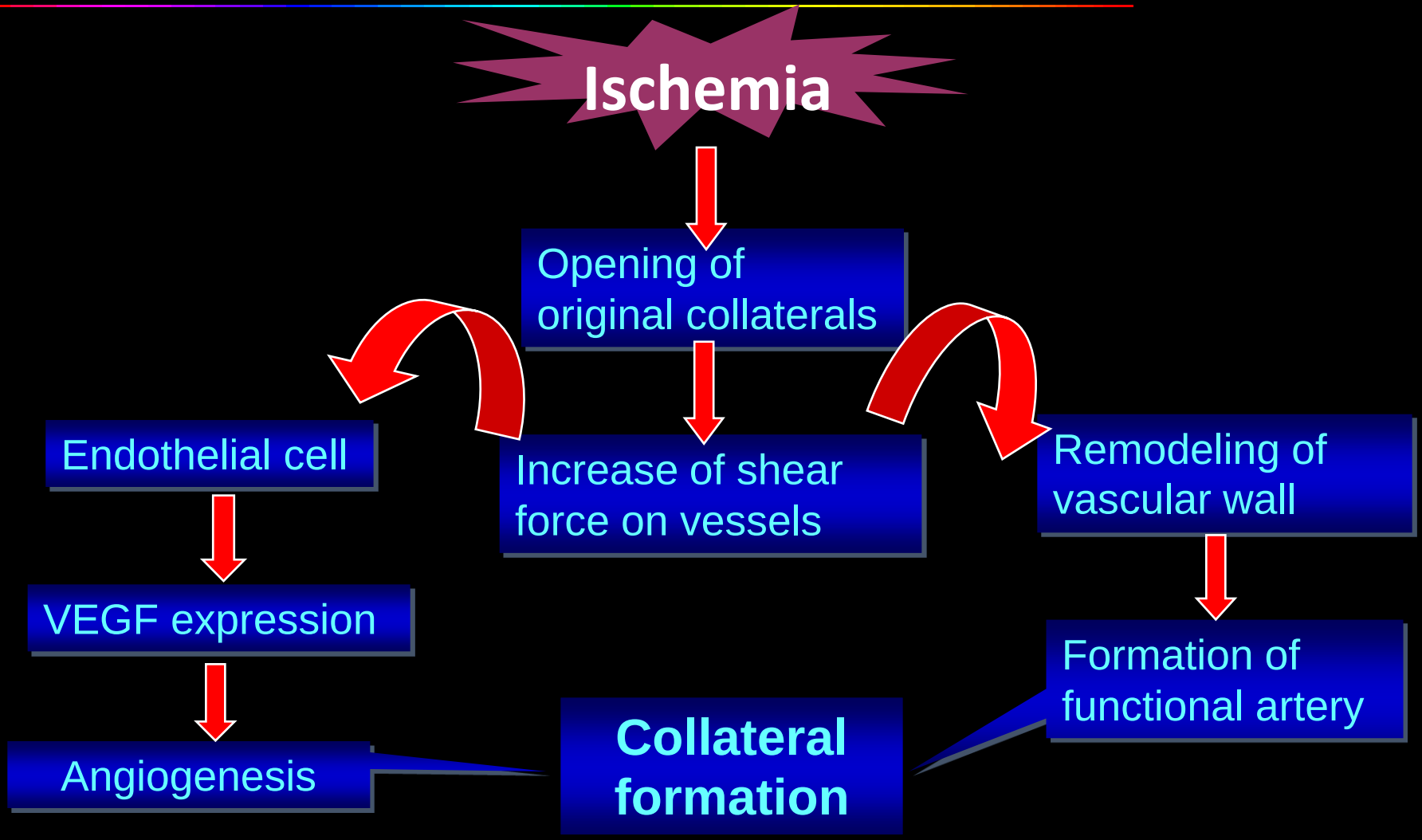
- **Requires**
  - Ischemic stimulation
  - Facilitators: vascular endothelial growth factors (VEGF)
  - Cells: endothelial progenitor cells (EPCs)
- **Clinical thinking**
  - What would be a safe way to promote collateral formation without risk of tissue necrosis?

Hypothesis:

Physiologic ischemic training - bio-bypass by collateral formation

- Collateral formation induced by repeated Ischemic episode of skeletal muscle by **cuff compression** or **isometric contraction**.
- **Mechanism: ischemia may induce auto-protection phenomenon to facilitate vascular formation factors (VEGF) and homing of stem cell (EPCs), which may lead to collateral formation at ischemic area. This is so called arterial bio-bypass.**
- To be confirmed: effectiveness, safety and applicability
- Serial studies during past 16 years.

Mechanism of collateral formation



Study clue: Ischemic preconditioning

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium.

C E Murry, R B Jennings and K A Reimer

Circulation. 1986;74:1124-1136
doi: 10.1161/01.CIR.74.5.1124

Charles E. Murry

block of coronary artery in dogs following by reperfusion for 5 min may lead to increase of tolerance of myocardial ischemia. Repeated 4 times may reduce size of myocardial infarction (75%) by 40 min block of the artery following by reperfusion. 1986

Remote Ischemic preconditioning

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Regional ischemic 'preconditioning' protects remote virgin myocardium from subsequent sustained coronary occlusion.

K Przyklenk, B Bauer, M Ovize, R A Kloner and P Whittaker

Circulation. 1993;87:893-899
doi: 10.1161/01.CIR.87.3.893

Karin Przyklenk

The effect of preconditioning phenomenon could be induced by remote approach in animal model from Przyklenk K et al in 1993.

Remote Ischemic preconditioning by other tissues

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

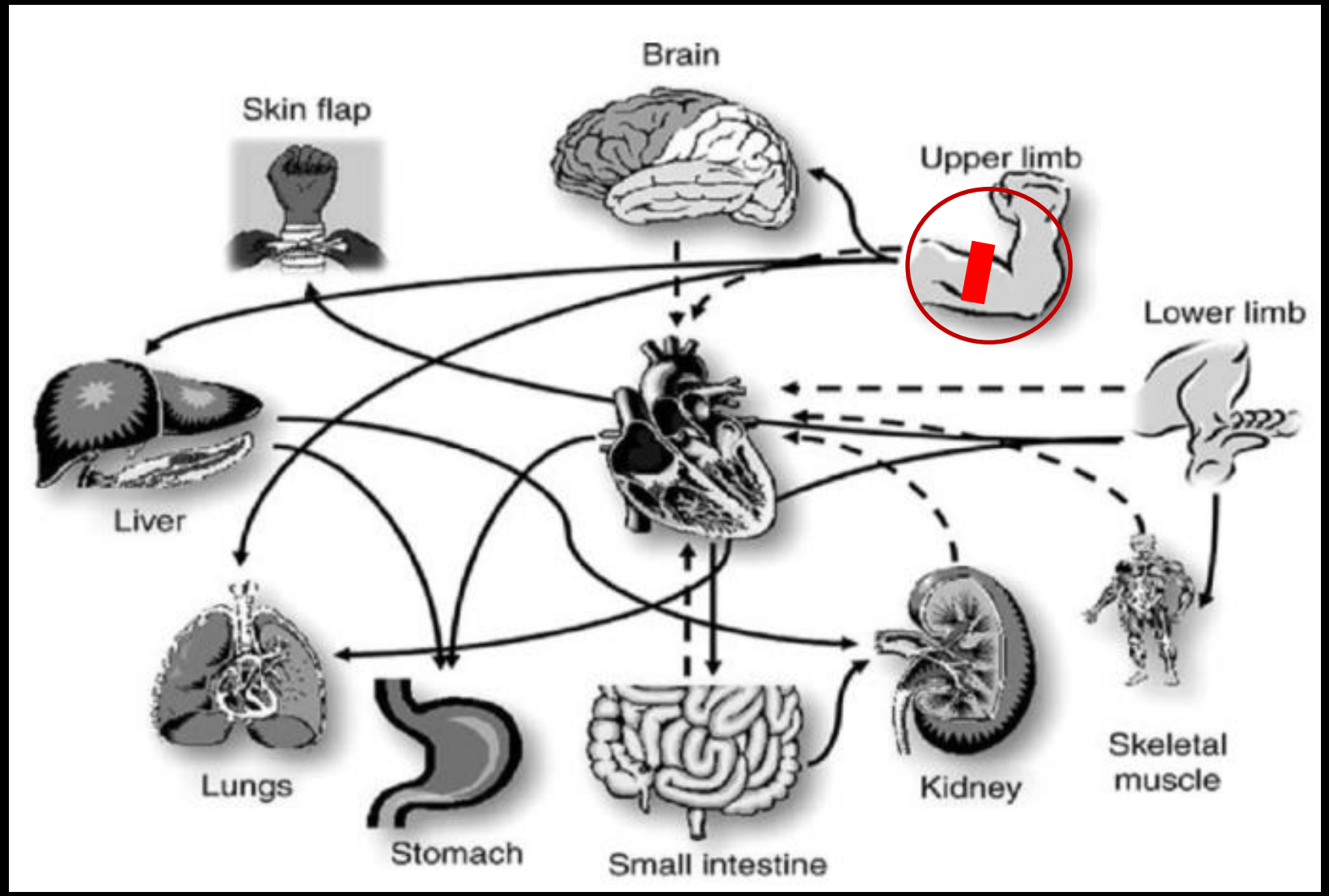
Transient Limb Ischemia Induces Remote Ischemic Preconditioning In Vivo

R.K. Kharbanda, U.M. Mortensen, P.A. White, S.B. Kristiansen, M.R. Schmidt, J.A. Hoschtitzky, M. Vogel, K. Sorensen, A.N. Redington and R. MacAllister

Circulation. 2002;106:2881-2883; originally published online November 18, 2002;
doi: 10.1161/01.CIR.0000043806.51912.9B

Following studies confirmed this remote phenomenon of transient ischemic preconditioning by limb in 2002.

Remote Ischemic preconditioning or training?



Remote preconditioning – role in neuro-protection 2011

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

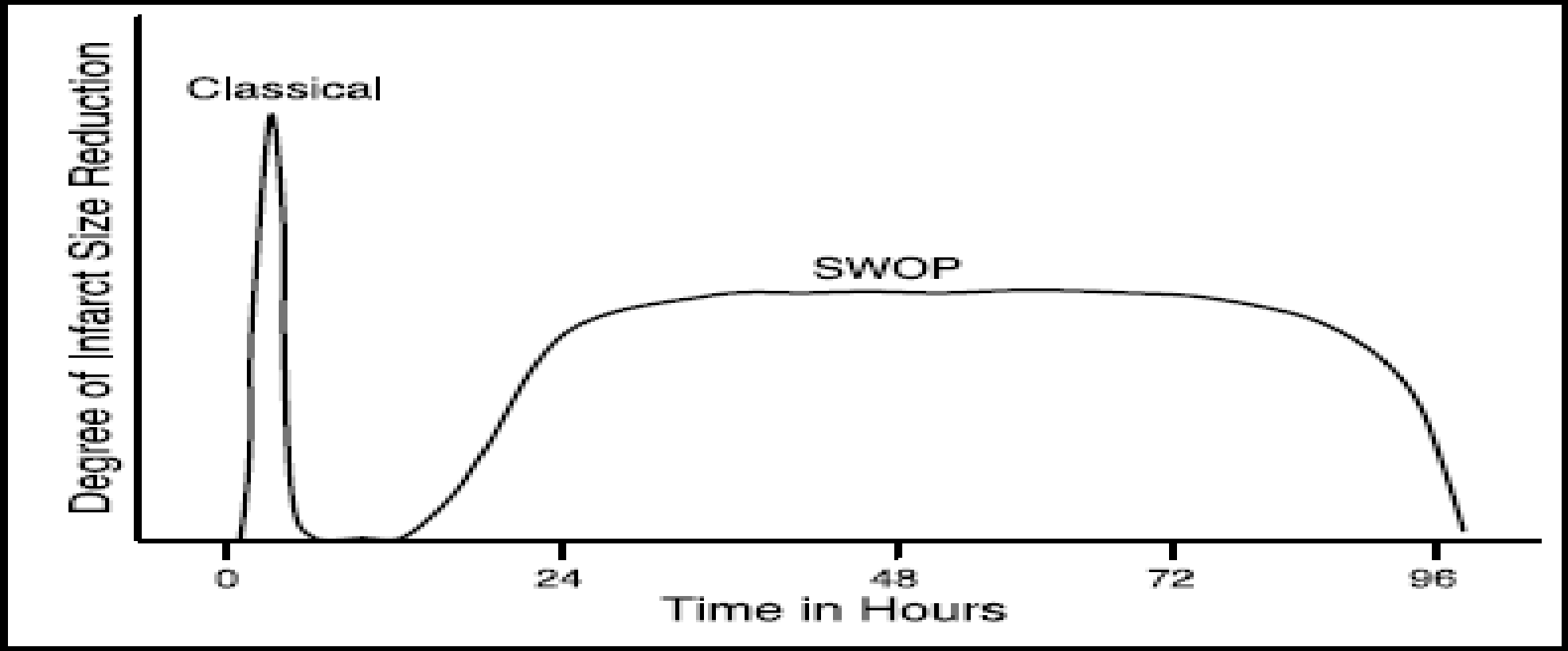
Remote Ischemic Preconditioning: Making the Brain More Tolerant, Safely and Inexpensively

Michael A. Moskowitz and Christian Waeber

Circulation. 2011;123:709-711; originally published online February 7, 2011;
doi: 10.1161/CIRCULATIONAHA.110.009688
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

Time window of preconditioning training



1. Fast effect: occurred few min post preconditioning, lasting for 1 to 2 hrs.
2. Delayed effect: 24-72 hrs post preconditioning and lasting 3-4 days

Physiol Rev 83: 1113–1151, 2003; 10.1152

Transit ischemic attack - preconditioning？

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association | American Stroke Association

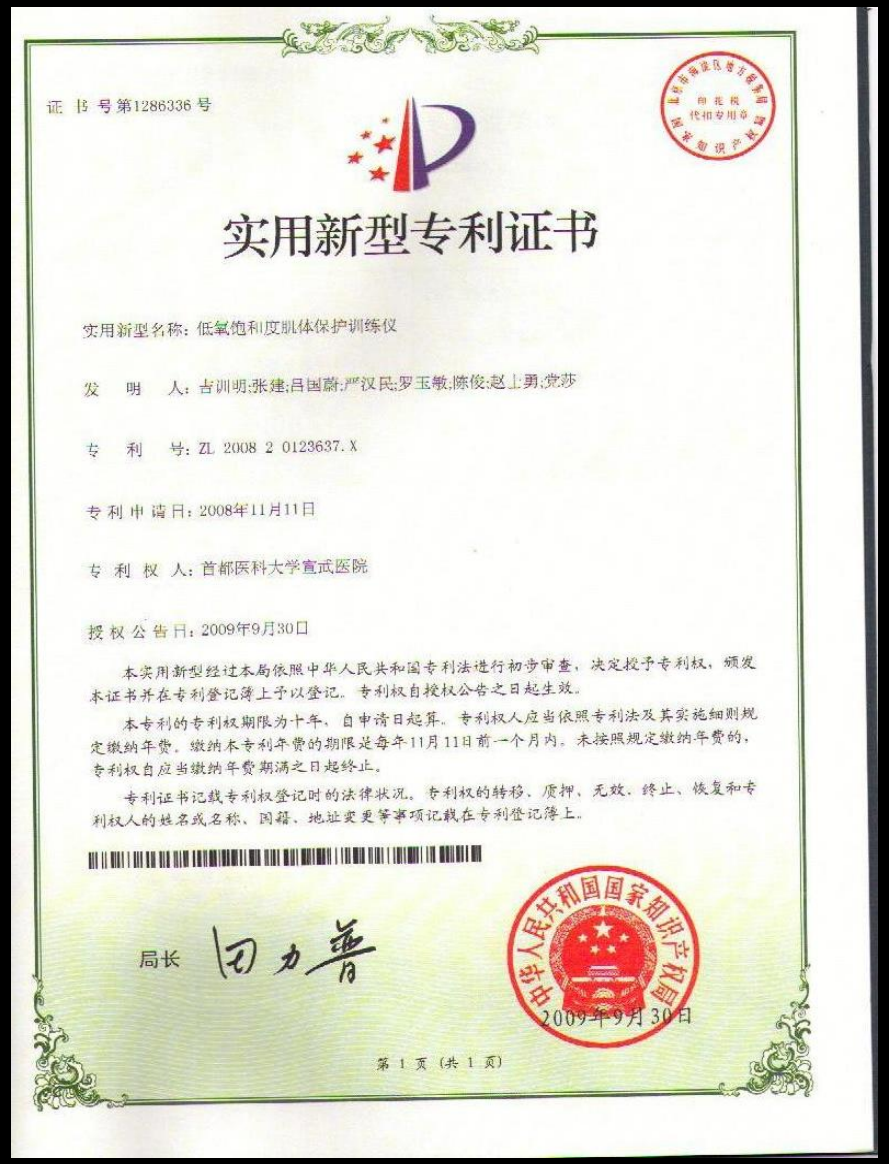
Transient Ischemic Attacks Before Ischemic Stroke: Preconditioning the Human Brain?: A Multicenter Magnetic Resonance Imaging Study

Susanne Wegener, Barbara Gottschalk, Verica Jovanovic, René Knab, Jochen B. Fiebach, Peter D. Schellinger, Thomas Kucinski, Gerhard J. Jungehülsing, Peter Brunecker, Bianca Müller, Anna Banasik, Nicola Amberger, Klaus D. Wernecke, Mario Siebler, Joachim Röther, Arno Villringer and Markus Weih

Stroke. 2004;35:616-621; originally published online February 12, 2004;
doi: 10.1161/01.STR.0000115767.17923.6A

65 cases, first attack of stroke (ischemic), infarction size is small in pts with TIA (16 cases) than in pts without （49 cases) (9.1mL vs 36.5mL， p=0.014)

China innovation by Dr. Ji Xunming



证书号第1286336号

实用新型专利证书

实用新型名称：低氧饱和度肌体保护训练仪

发明人：吉训明;张建;吕国蔚;严汉民;罗玉敏;陈俊;赵上勇;党莎

专利号：ZL 2008 2 0123637.X

专利申请日：2008年11月11日

专利权人：首都医科大学宣武医院

授权公告日：2009年9月30日

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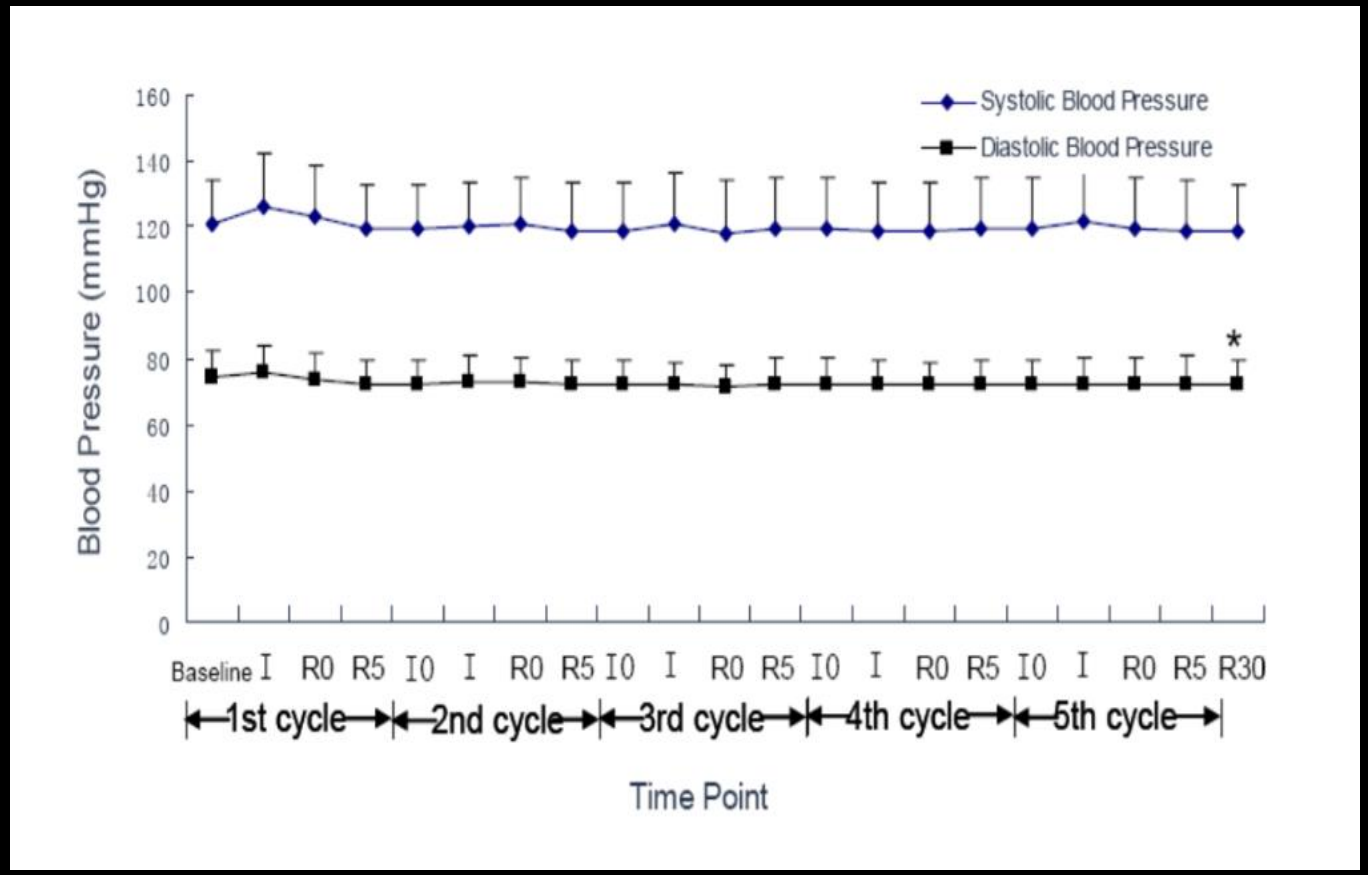
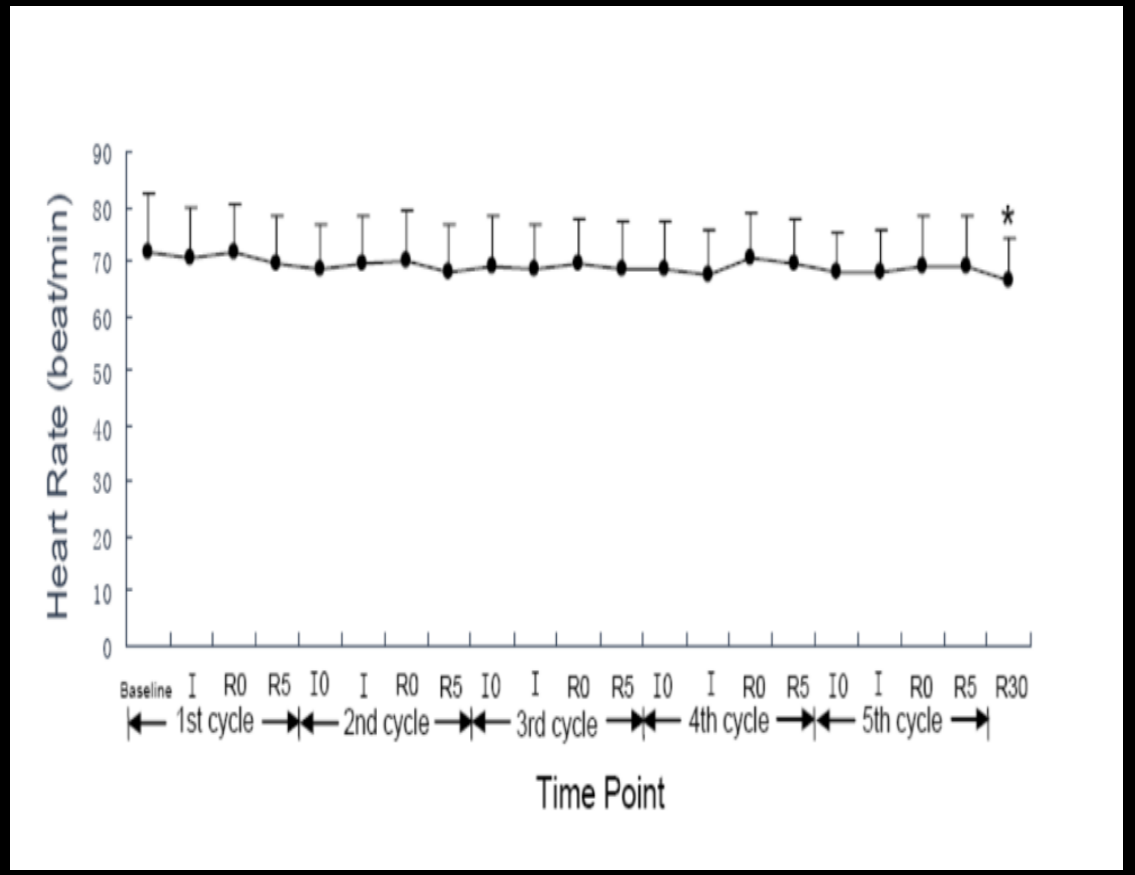
2009年9月30日

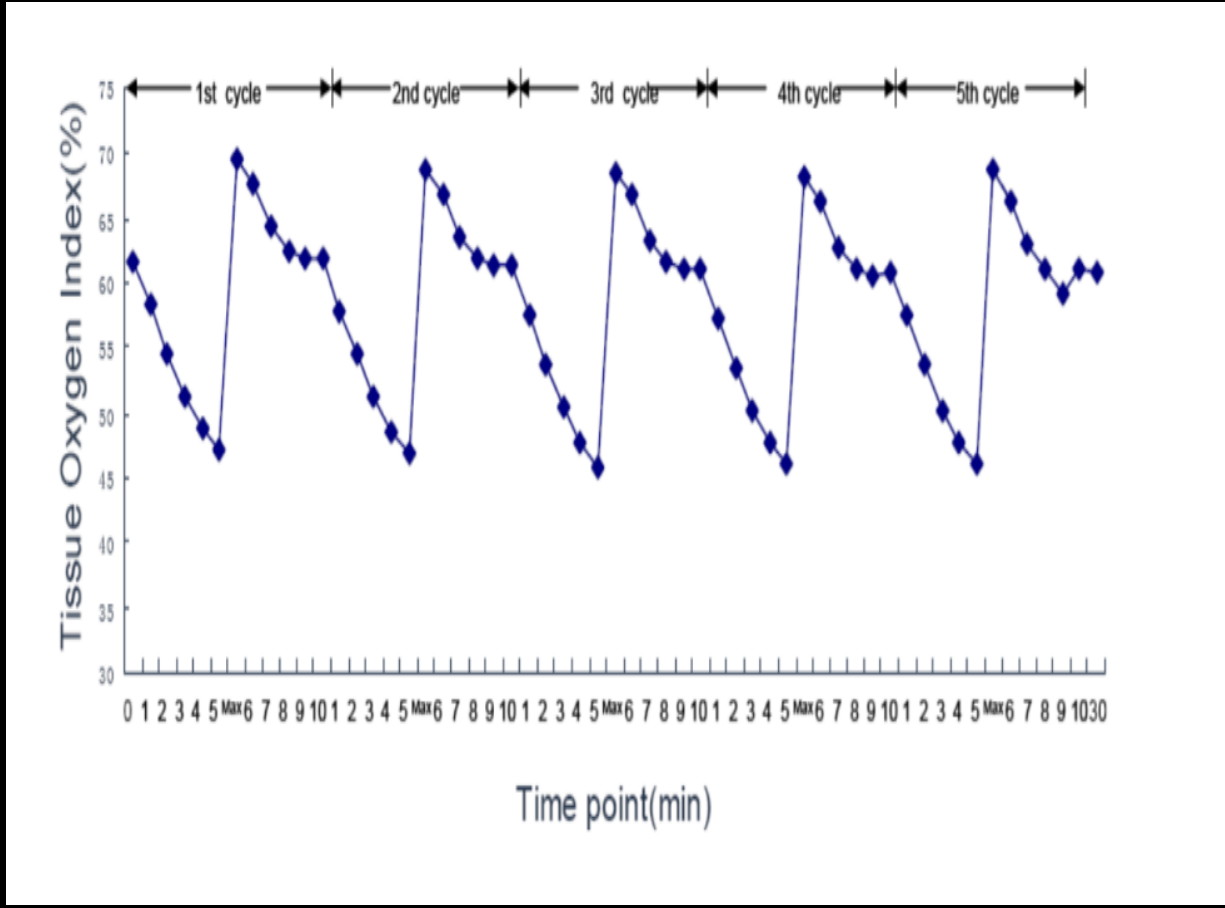
第 1 页（共 1 页）

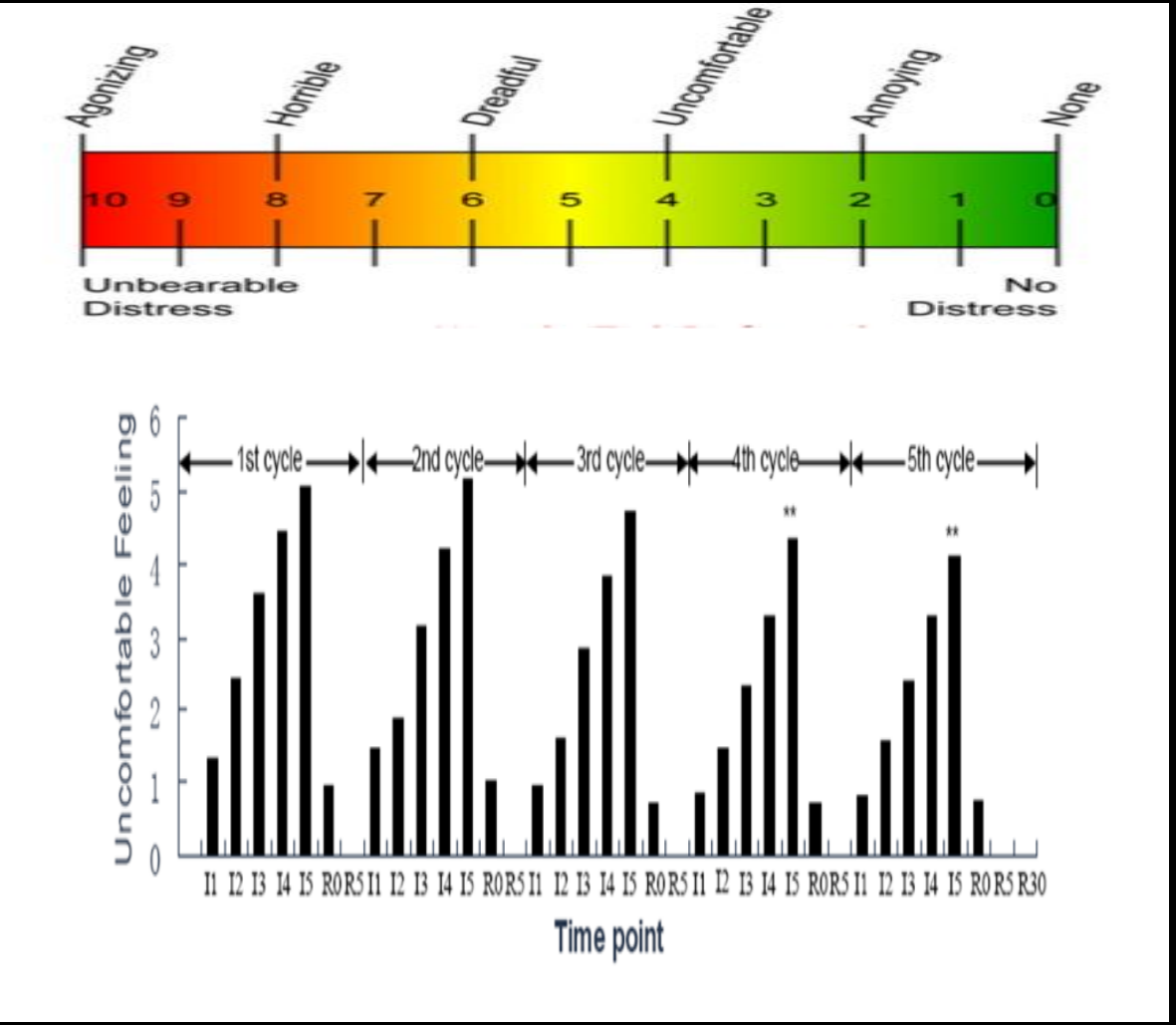
Safety-remote preconditioning



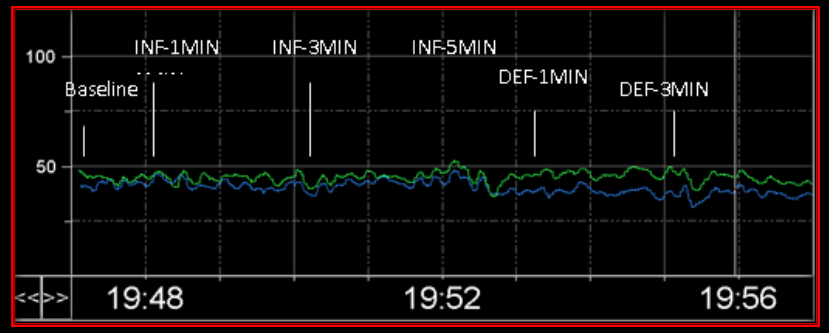


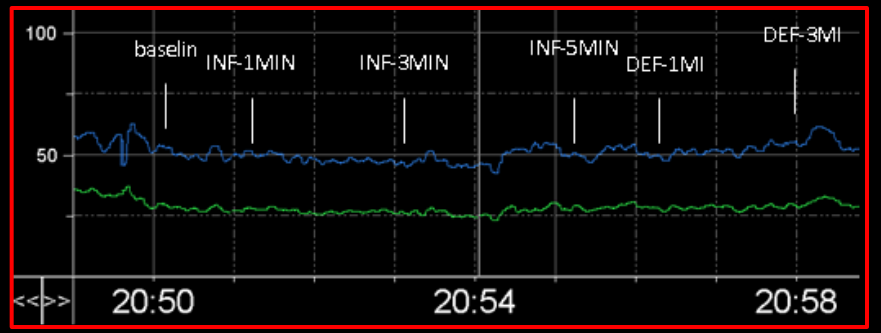
Safety-remote preconditioning

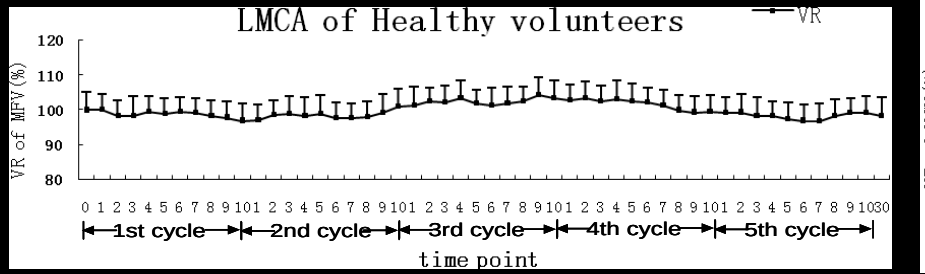


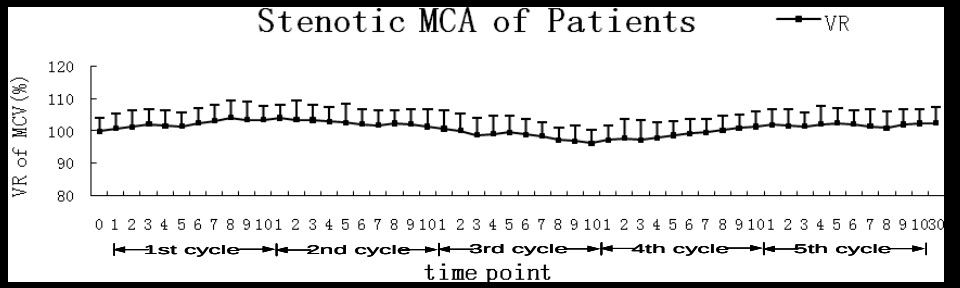


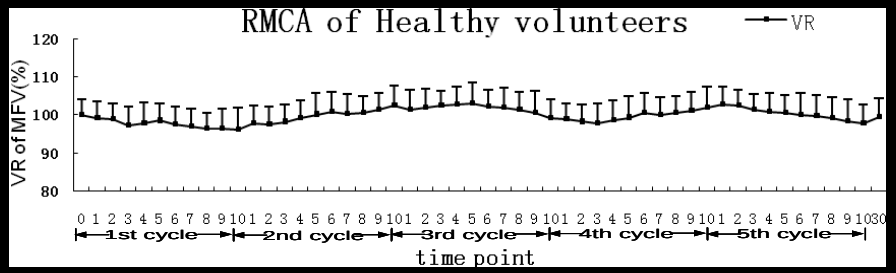
Safety-remote preconditioning

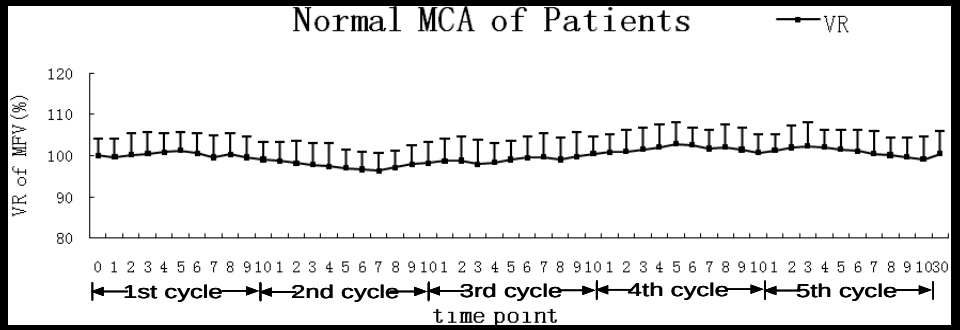












No influence on brain blood flow

Effectiveness in patients with stroke

Upper limb ischemic preconditioning prevents recurrent stroke in intracranial arterial stenosis

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Yu Liu, MD
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ABSTRACT

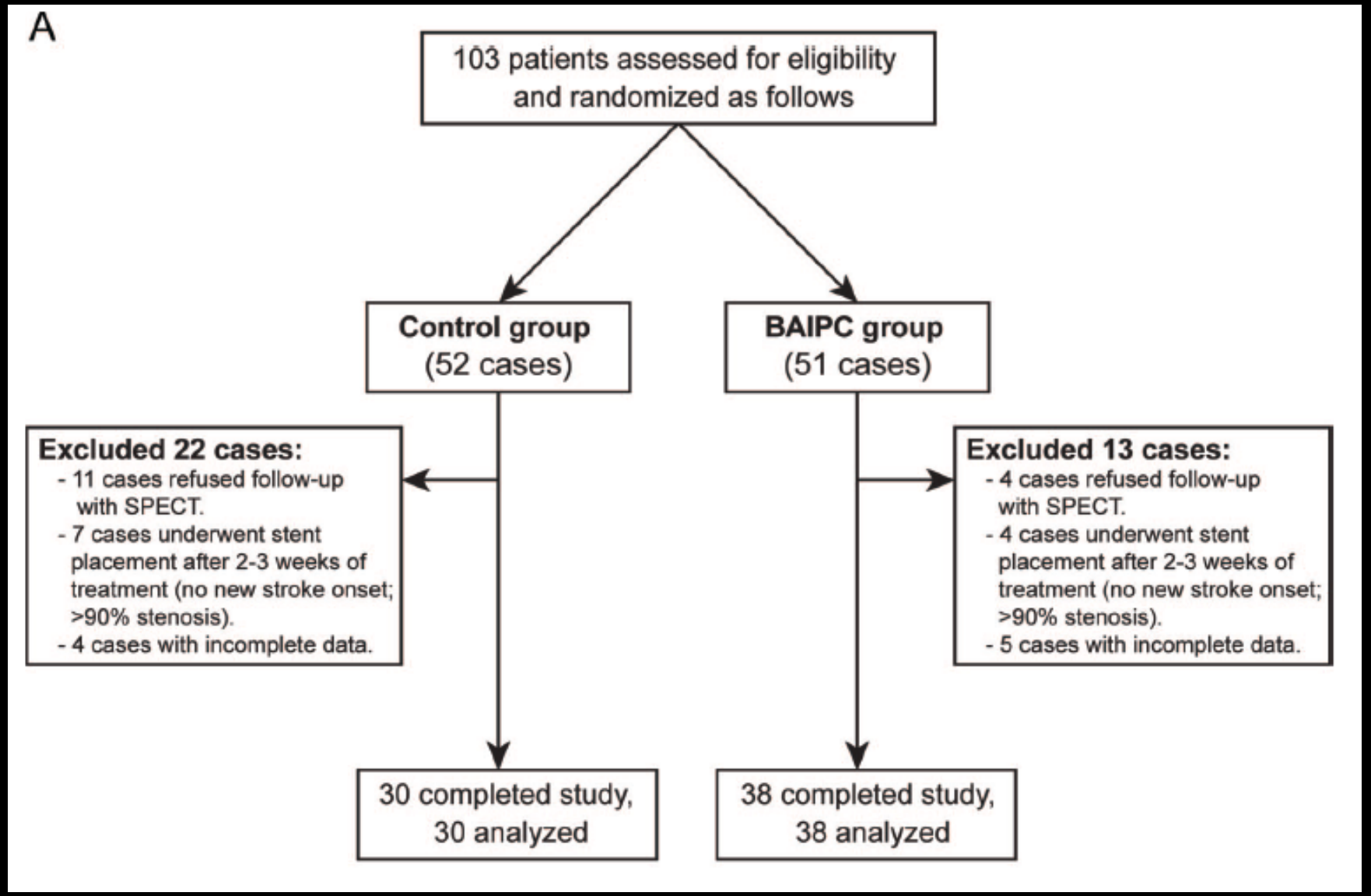
Objective: This study aims to evaluate protective effects of brief repetitive bilateral arm ischemic preconditioning (BAIPC) on stroke recurrence in patients with symptomatic atherosclerotic intracranial arterial stenosis (IAS).

Methods: A total of 68 consecutive cases with symptomatic IAS, diagnosed by imaging, were enrolled in this prospective and randomized study. All patients received standard medical management. Patients in the BAIPC group (n = 38) underwent 5 brief cycles consisting of bilateral upper limb ischemia followed by reperfusion. The BAIPC procedure was performed twice daily over 300 consecutive days. Incidence of recurrent stroke and cerebral perfusion status in BAIPC-treated patients were compared with the untreated control group (n = 30).

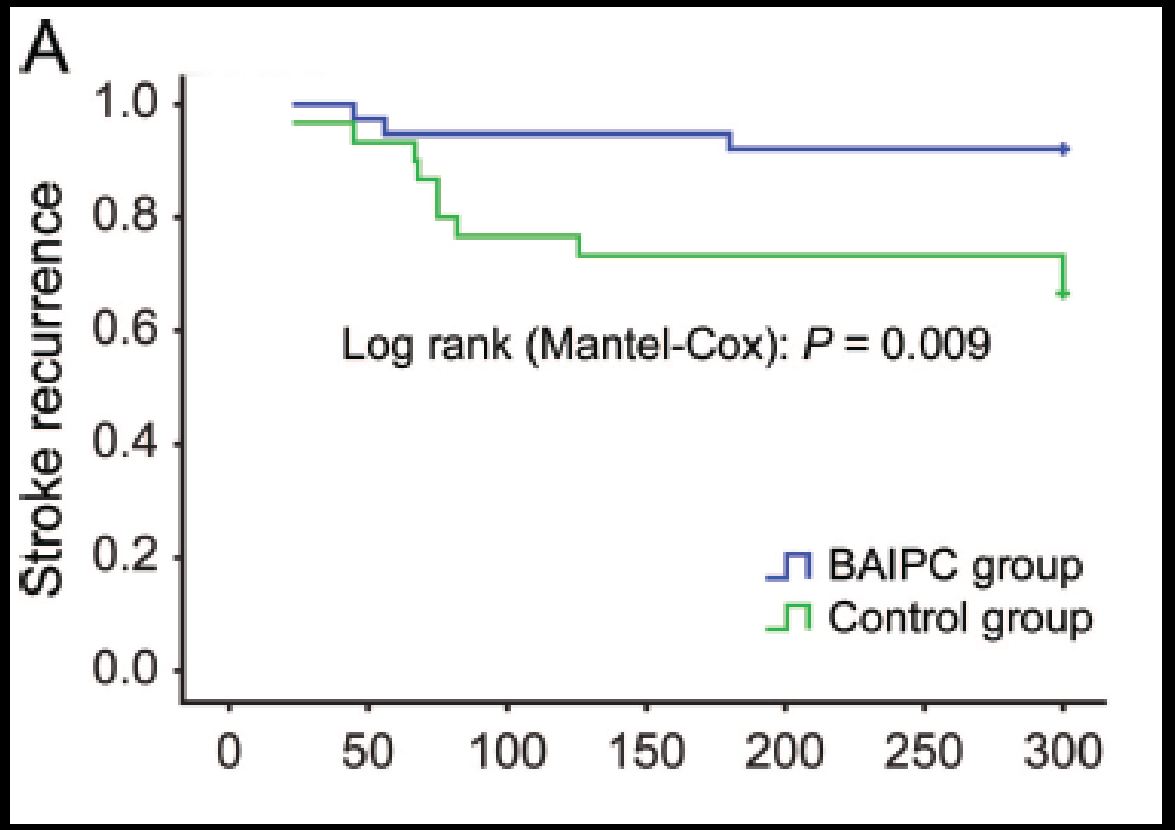
Results: In the control group, incidence of recurrent stroke at 90 and 300 days were 23.3% and 26.7%, respectively. In the BAIPC group, incidence of recurrent stroke was reduced to 5% and 7.9% at 90 and 300 days ($p < 0.01$), respectively. The average time to recovery (modified Rankin Scale score 0–1) was also shortened by BAIPC. Cerebral perfusion status, measured by SPECT and transcranial Doppler sonography, improved remarkably in BAIPC-treated brain than in control ($p < 0.01$).

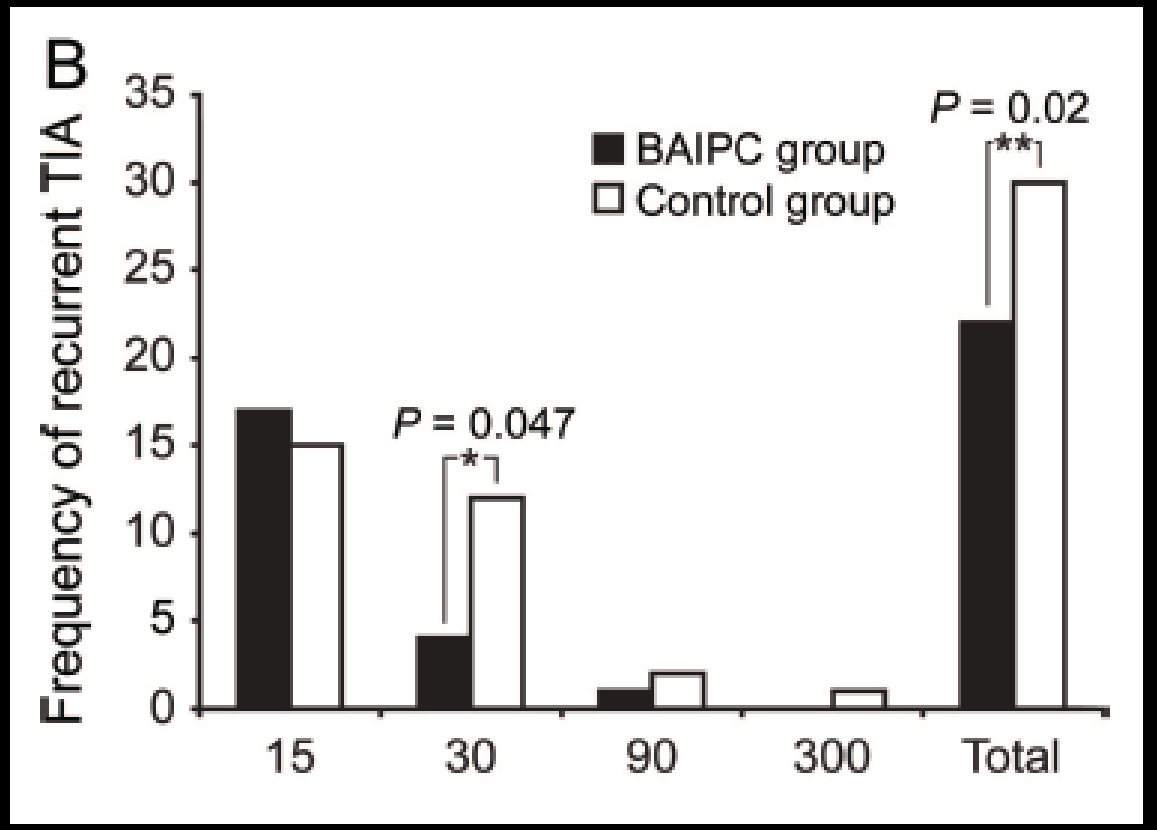
Conclusion: This study provides a proof-of-concept that BAIPC may be an effective way to improve cerebral perfusion and reduce recurrent strokes in patients with IAS. Further investigation of this therapeutic approach is warranted as some patients were excluded after randomization. *Neurology*® 2012;79:1853–1861

Study design



Recurrent rate of stroke and TIA





Observation of 300 days, stroke recurrent rate is lower in BAIPC Group than the control. TIA recurrent reduction is even lower.

Neurology Editorial

EDITORIAL

Preconditioning reaches clinical practice in intracranial arterial stenosis

Brad E. Zacharia, MD
Samuel S. Bruce, BA
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Neurology® 2012;79:1842–1843

Symptomatic atherosclerotic intracranial arterial stenosis is a common etiologic mechanism of ischemic stroke. Patients with intracranial arterial stenosis carry a high risk of recurrent stroke that persists even with aggressive preventive measures.[1] The growing popularity of endovascular interventions for intracranial arterial stenosis, such as percutaneous transluminal angioplasty and stenting (PTAS), has spurred hope that such an approach might reduce stroke recurrence and the substantial resulting morbidity. While not without its controversies, the recently presented results of the SAMMPRIS study (ClinicalTrials.gov number NCT00576693), a randomized controlled trial comparing aggressive medical management to PTAS in patients with intracranial arterial stenosis and recent stroke or TIA, found that PTAS might actually increase the risk of stroke recurrence.[2] Consequently, a demand endures for alternative therapies to reduce recurrent stroke risk in intracranial arterial stenosis.

device invented by the authors. The control group received standard medical therapy.

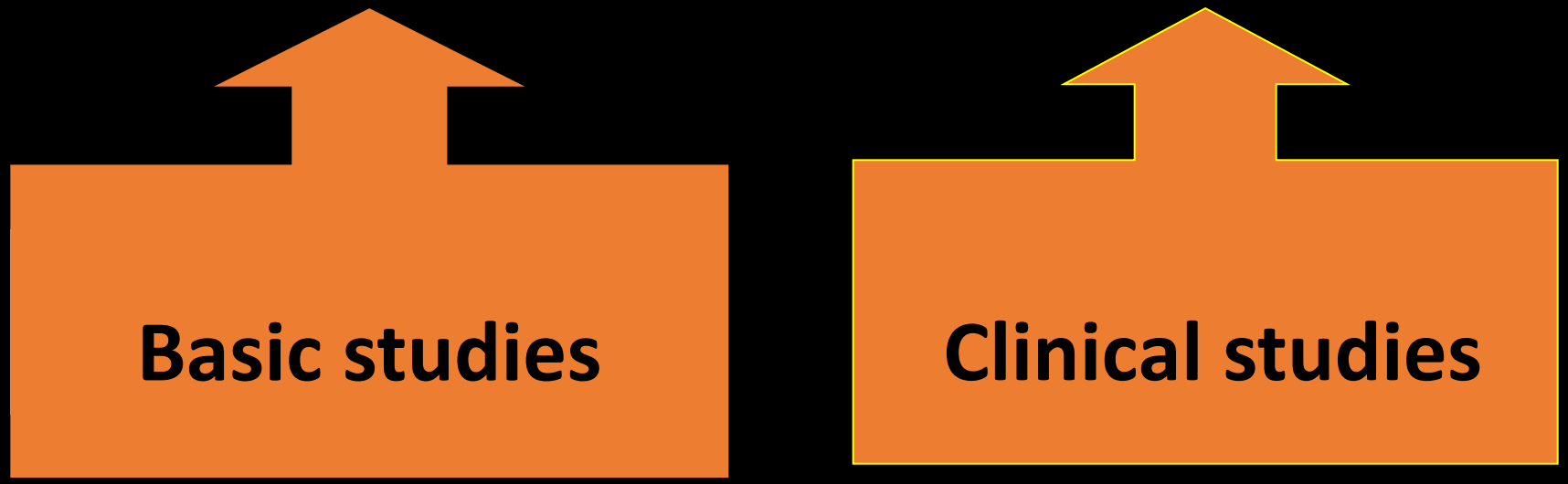
At both 90 and 300 days following randomization, the rates of recurrent stroke were reduced in the BAIPC group compared to the control group. Transcranial Doppler ultrasonography and perfusion SPECT also demonstrated improvements in cerebral blood flow and perfusion in the treatment cohort compared to the control. These results are promising and provide much-needed human data to support the efficacy of ischemic preconditioning in preventing recurrent stroke among patients with symptomatic intracranial arterial stenosis. In the wake of SAMMPRIS, such studies will be critical in advancing strategies to ameliorate the burden of recurrent stroke in these patients. These results should inform future trials, which should expand on the ideas and concepts illustrated here.

Despite the intriguing implications of this study,

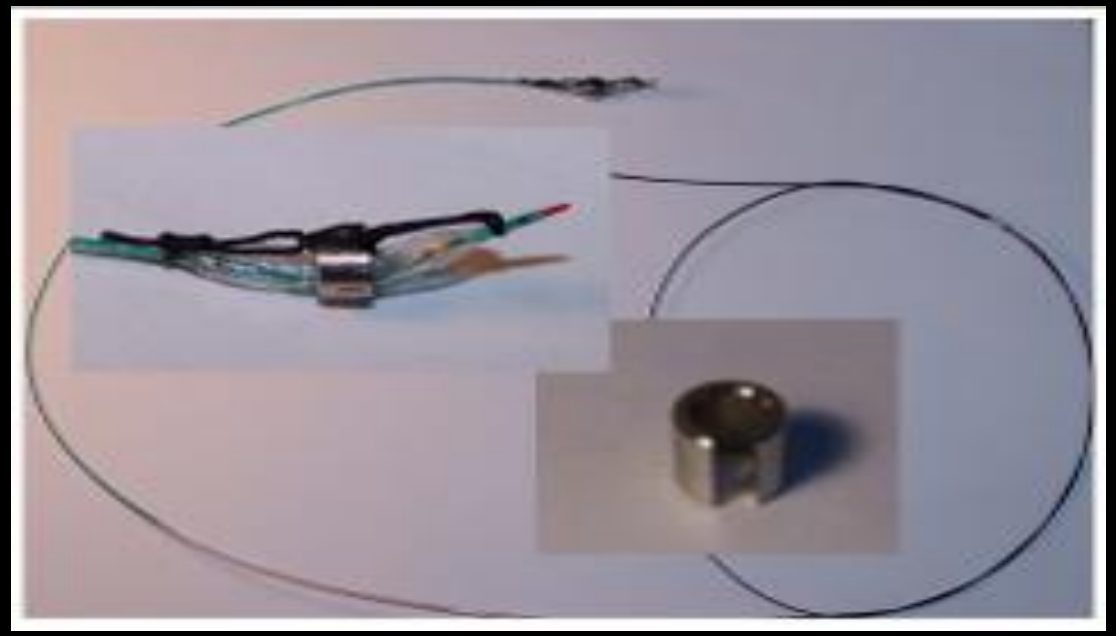
Comments

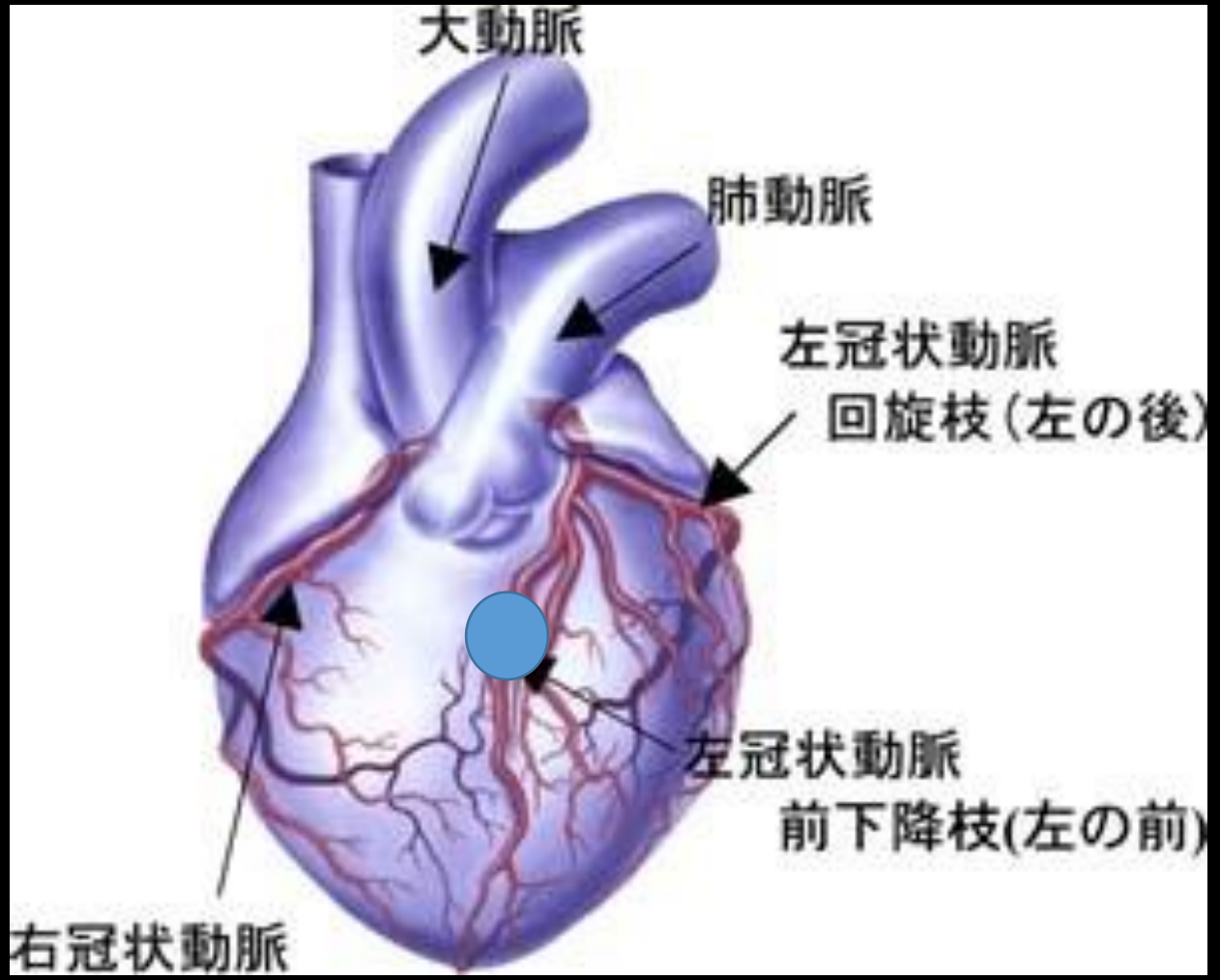
Our Studies in cardiac rehabilitation

Hypothesis: appropriate myocardial ischemia may facilitate collateral formation, thus to increase cardiac function

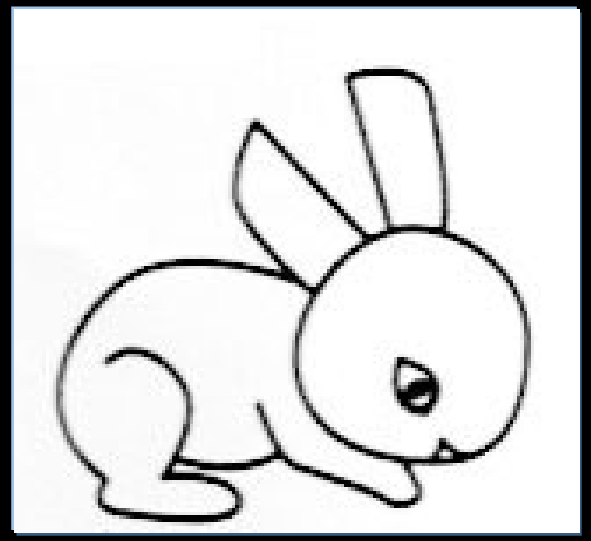


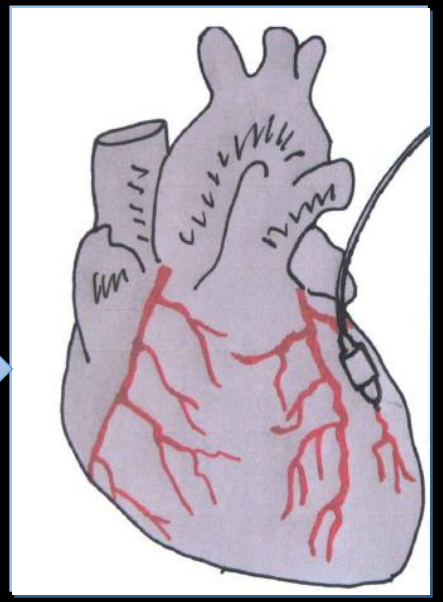
Model of chronic coronary artery stenosis by amyloid constrictor

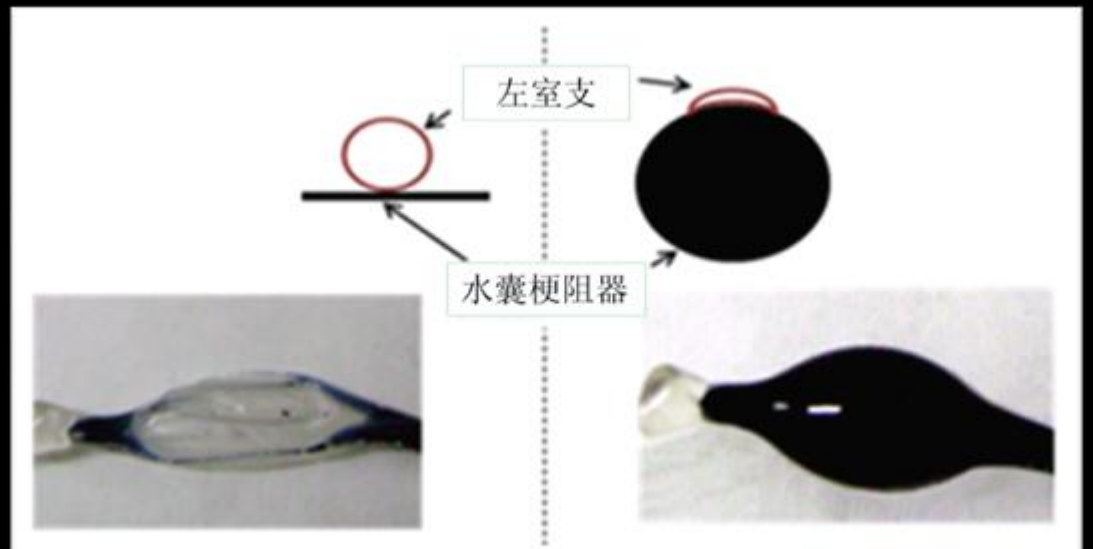




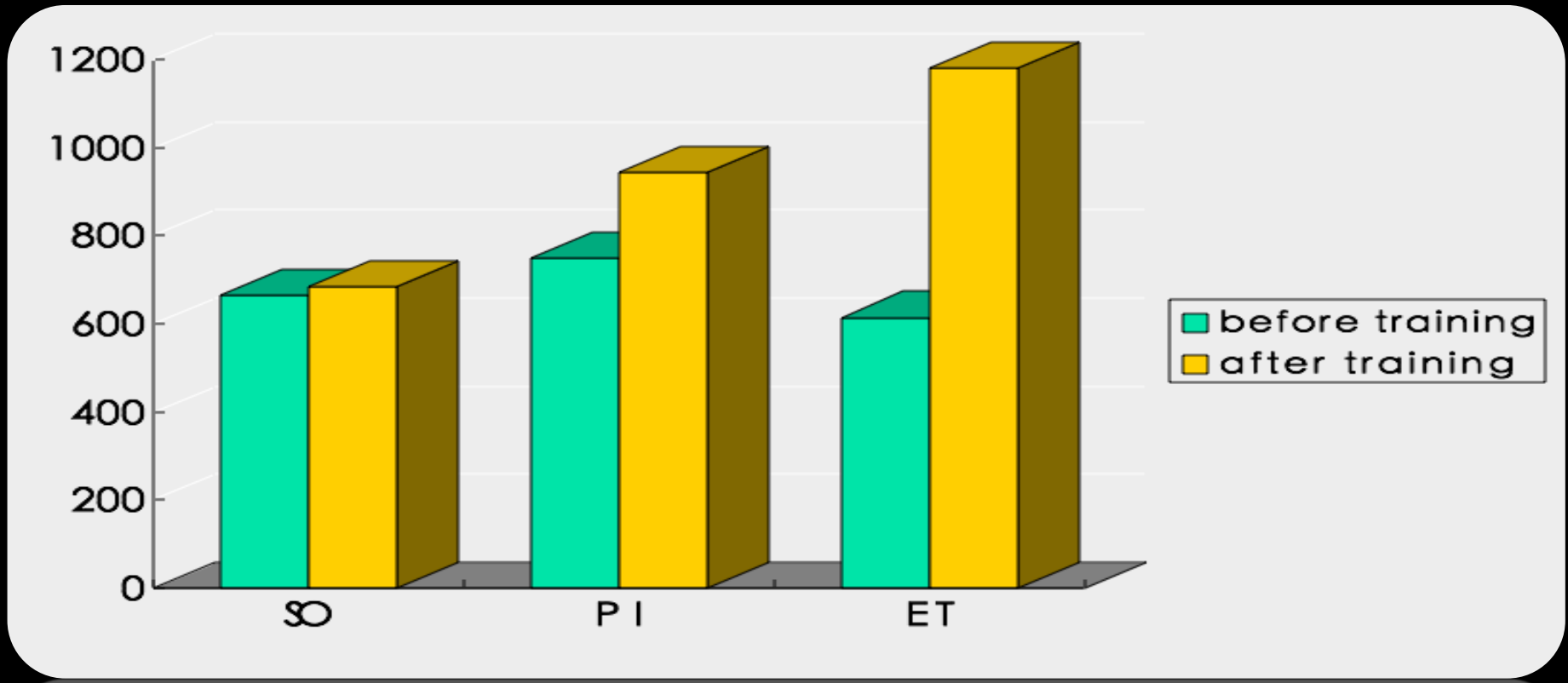
Controllable myocardial ischemia by a balloon catheter







Myocardial regional blood flow (microspheres/g)



- Finding: High intensity exercise training may facilitate LAD collateral formation and exercise capacity significantly compared with sham operation and pure myocardial ischemia in the model of chronic coronary artery stenosis in mini pig

However

- Intensive exercise may condition the myocardial have risk of myocardial over-load and lead to myocardial infarction, which is ethically and clinically not applicable in patients.
- Can we use the findings of ischemic conditioning for cardiac rehab training?

Remote effect of physiological ischemia training (PIT) on myocardial collateral formation

- Our studies found that in the animal model of repeated myocardial ischemia, VEGF was increased in other tissues, including liver, lung, brain and skeletal muscles.
- Our hypothesis: Repeated skeletal muscle ischemia may facilitate release of VEGF and EPCs and other regulatory factors to facilitate collateral formation in a myocardial ischemia region.

Lin A, Li J, Zhao Y et al. Effect of physiologic ischemic training on protection of myocardial infarction in rabbits. Am J Phys Med Rehabil. 2011 Feb; 90(2): 97-105.

Preconditioning or physiological ischemic training (PIT)?

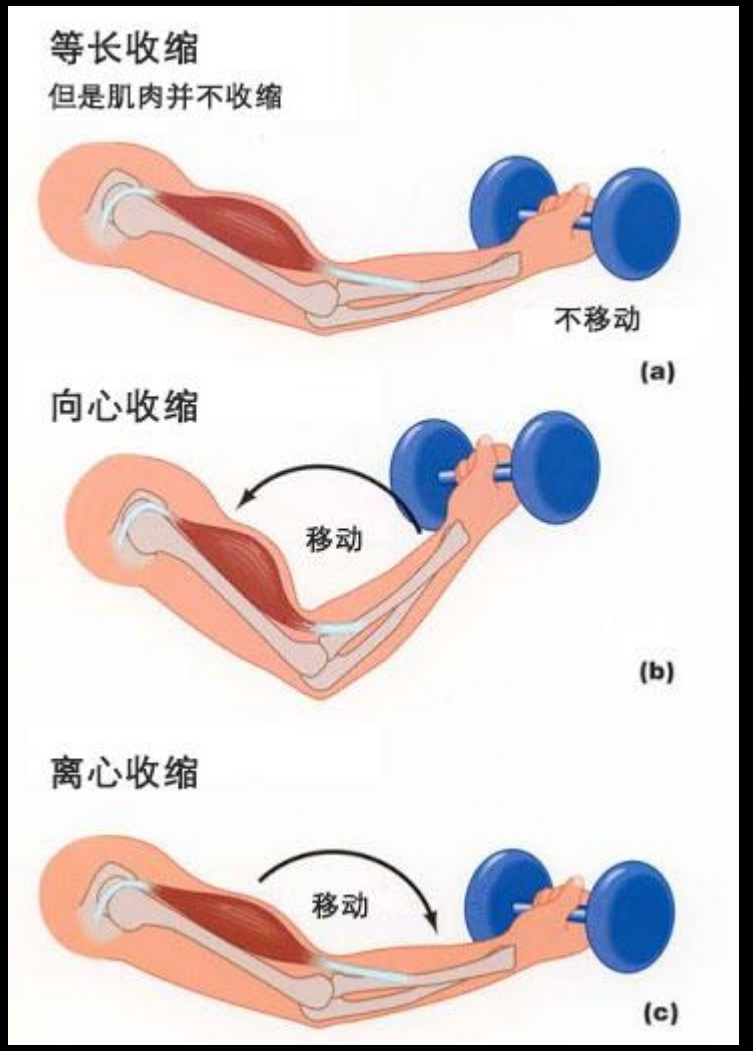
Preconditioning

- Method: repeated short time blood flow block
- Repetition: a few times
- Outcome: increase tolerance with ischemia
- Effective time: hours or days

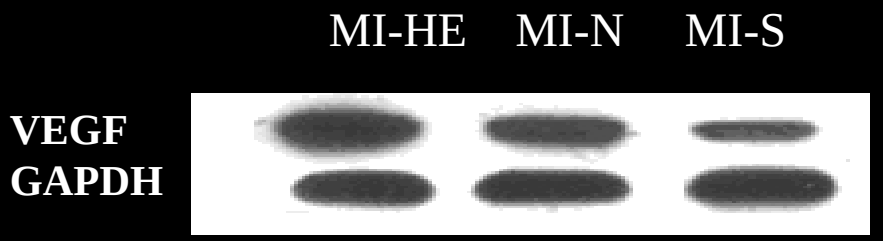
- PIT
  - Method: repeated short time blood flow block
  - Repetition: many for weeks
  - Outcome: increase collateral formation and tolerance with ischemia
  - Effective time: long term

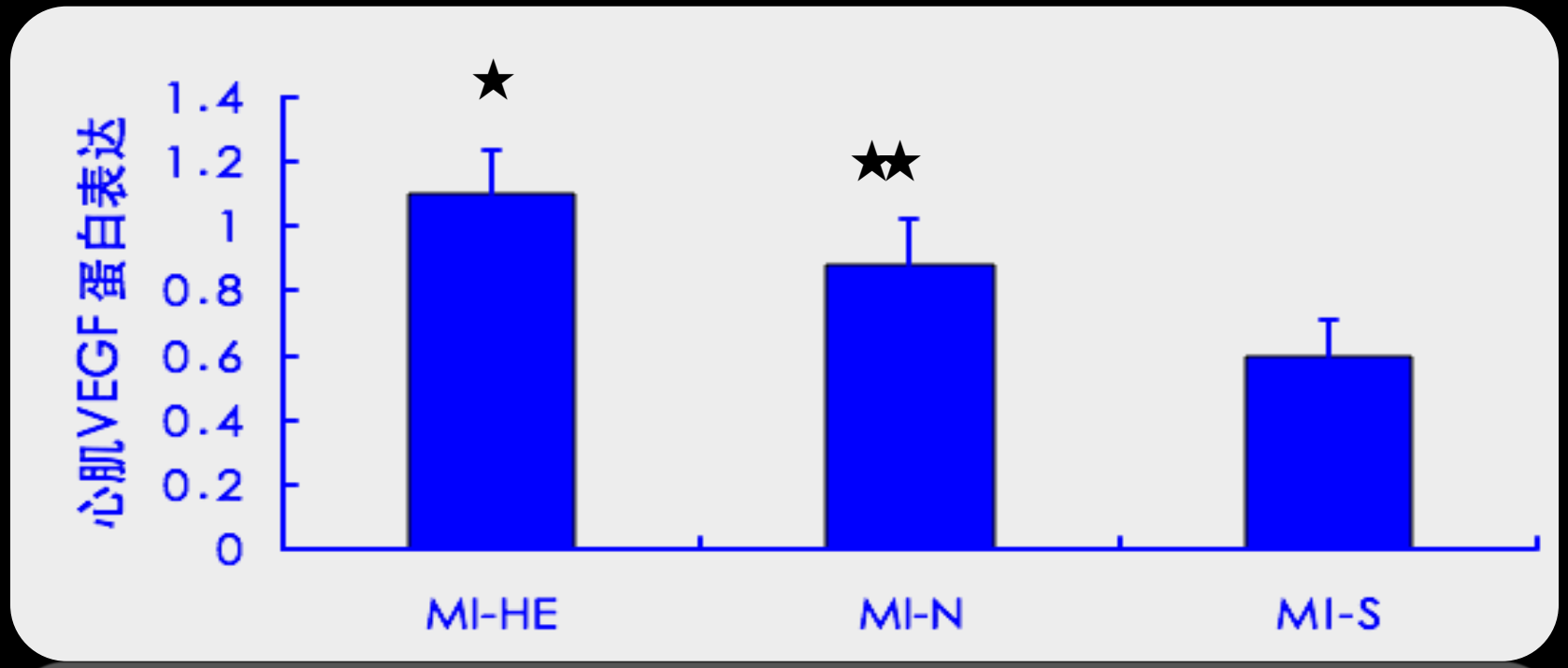
Method of physiological ischemia training

- **Cuff**
- **Isometric contraction**



VEGF in myocardium



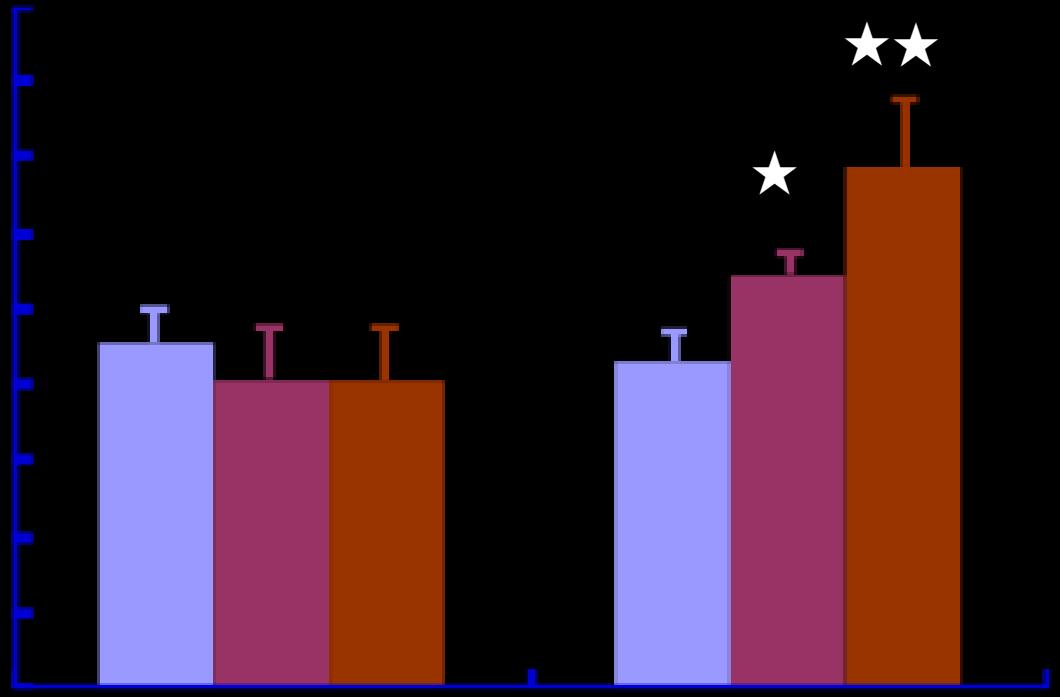


★★ MI-HE Vs MI-S P<0.01 ;

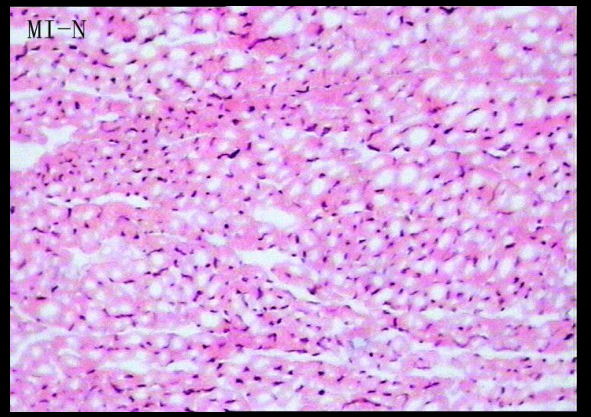
★ MI vs MI-S P<0.05

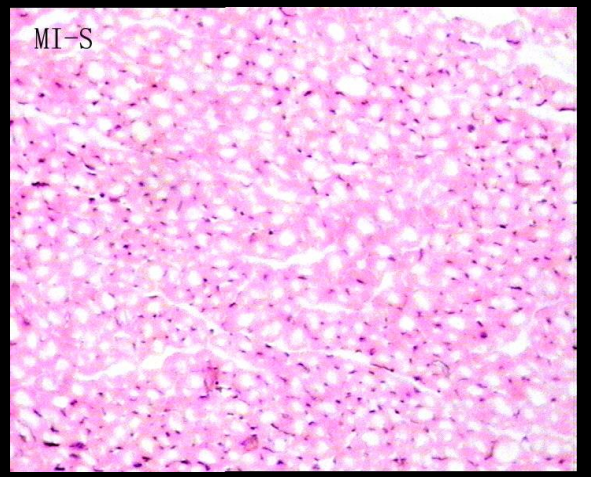
Myocardium regional blood flow

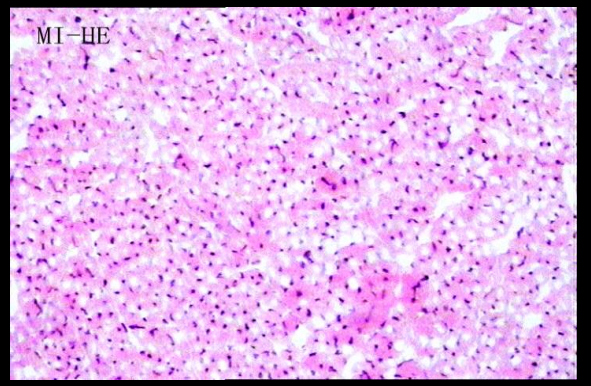
RIT: remote ischemic training
MI: Pure ischemia
Sham: sham operation



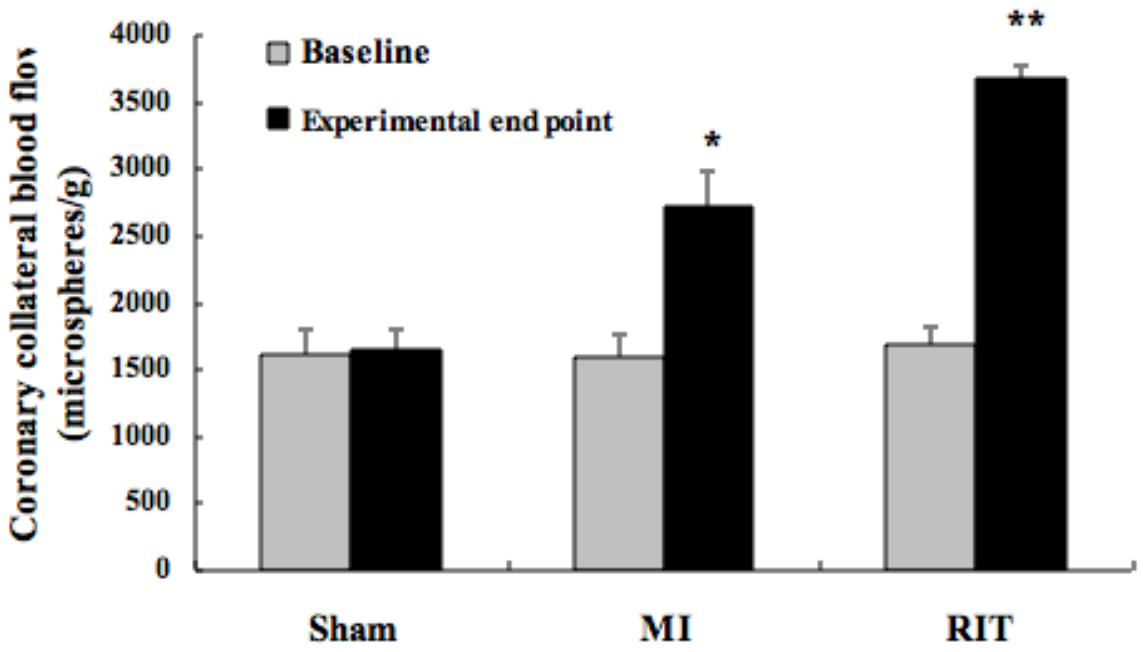
★ compared with Sham ***P*<0.01** ;
★★Compared with pure ischemia ***P*<0.01**



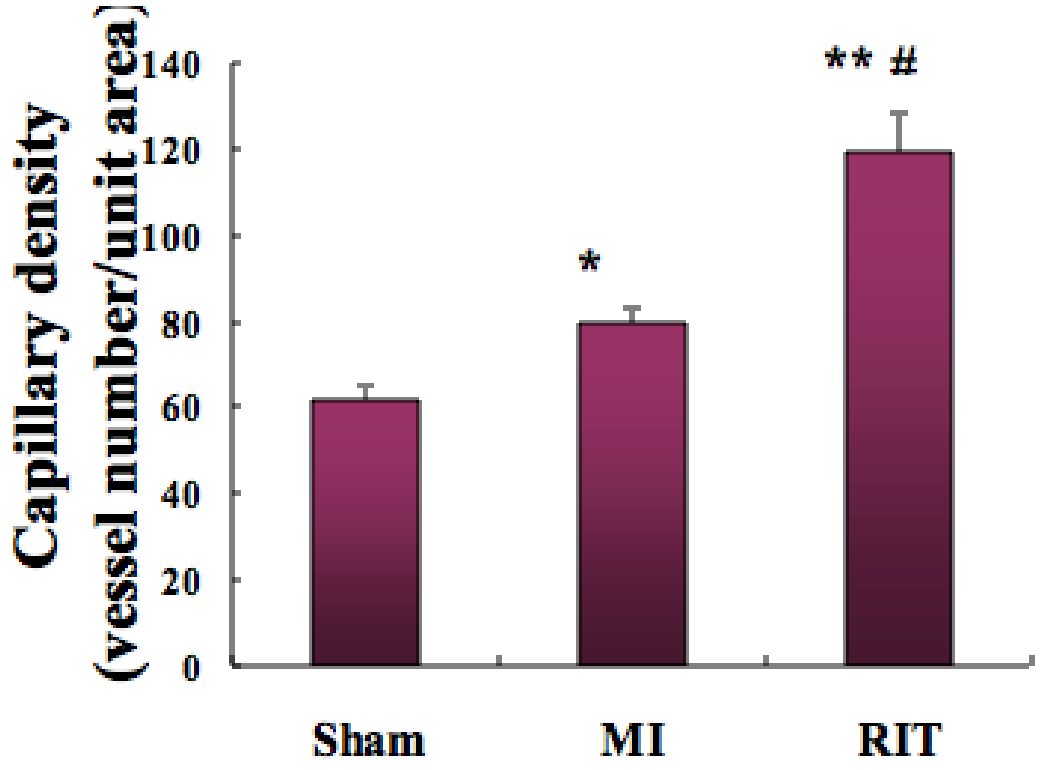




Regional blood flow



Density of capillaries

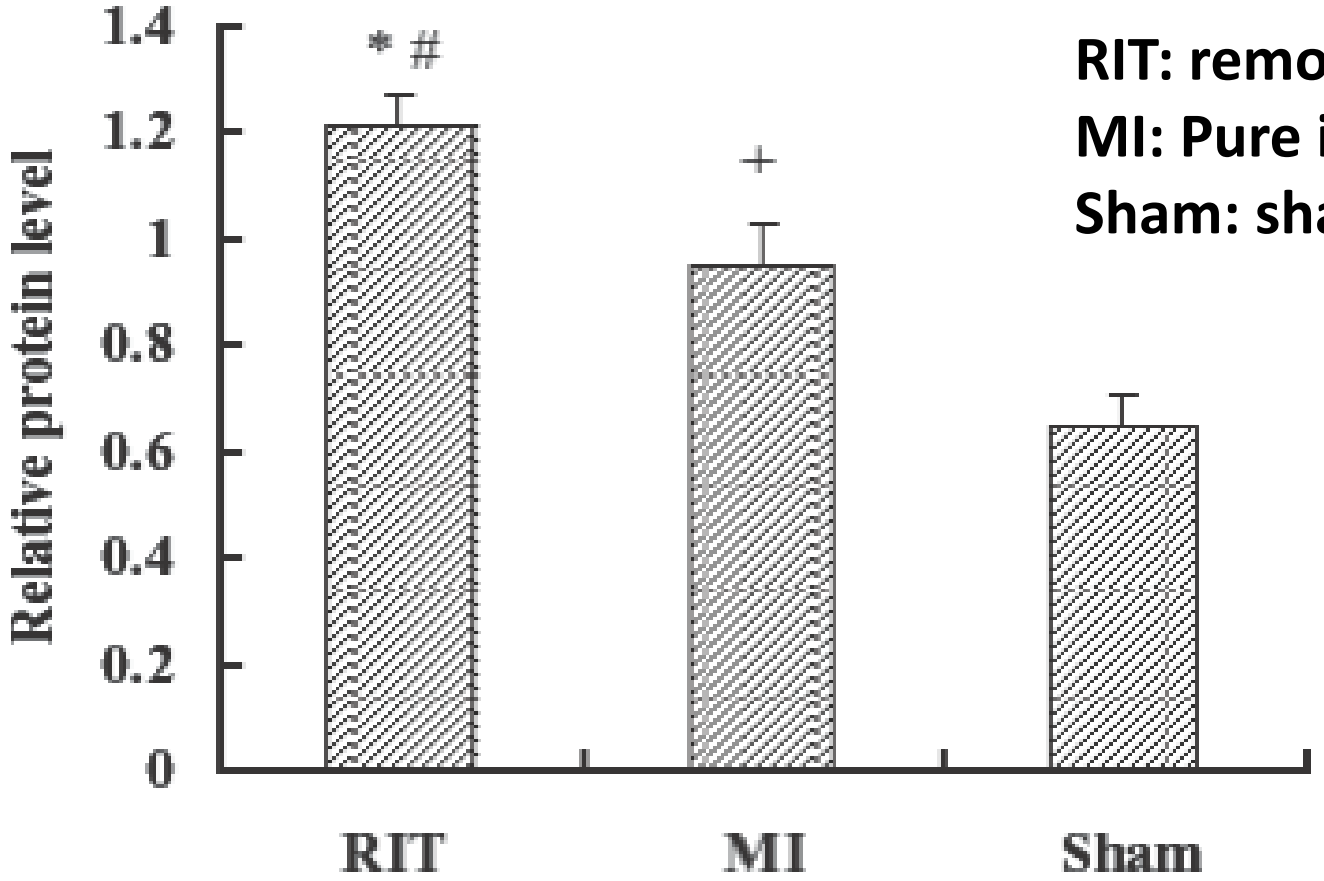


RIT: remote ischemic training

MI: Pure ischemia

Sham: sham operation

VEGF in Myocardium



RIT: remote ischemic training
MI: Pure ischemia
Sham: sham operation

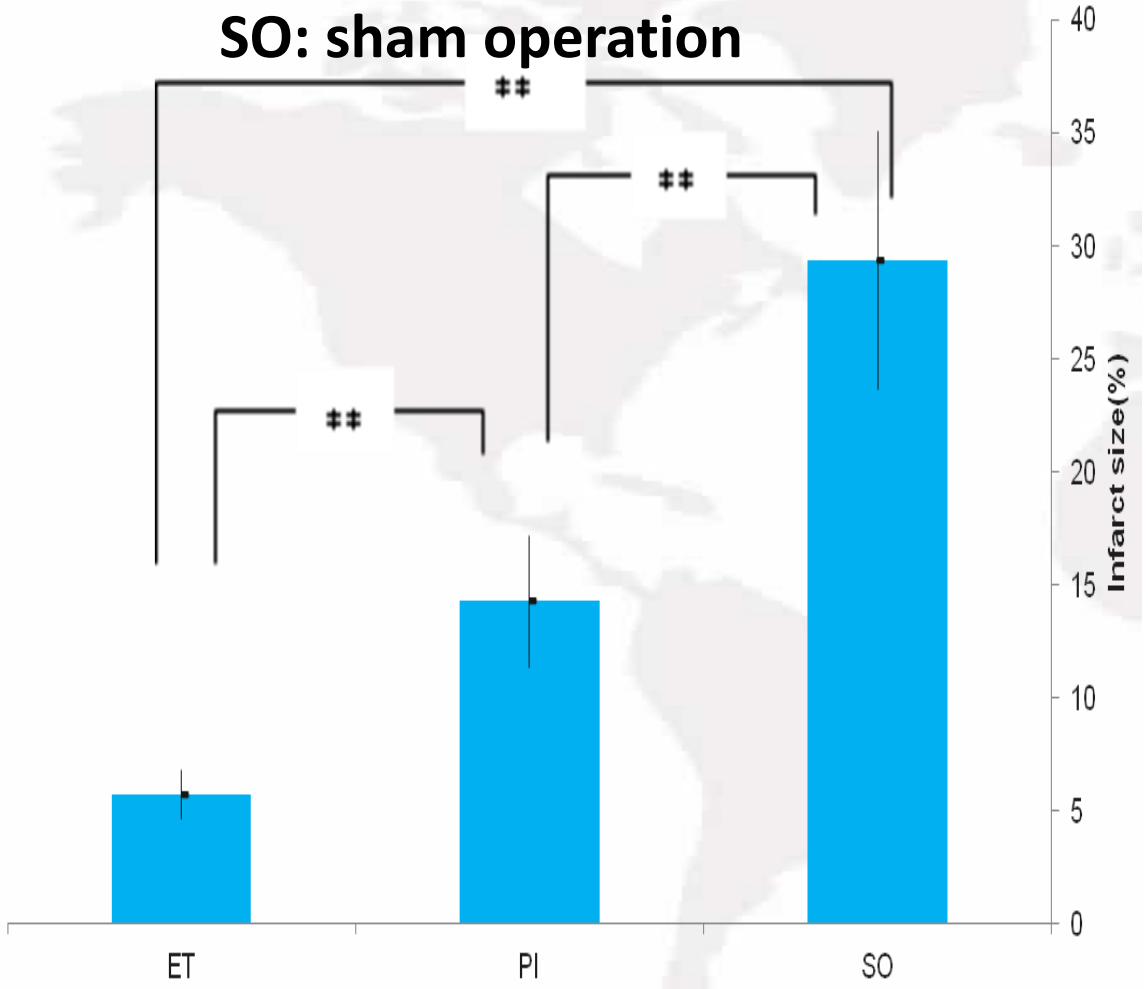
VEGF expression, * $P<0.05$ *vs* MI; + $P<0.01$ *vs* Sham; # $P<0.001$ *vs* Sham

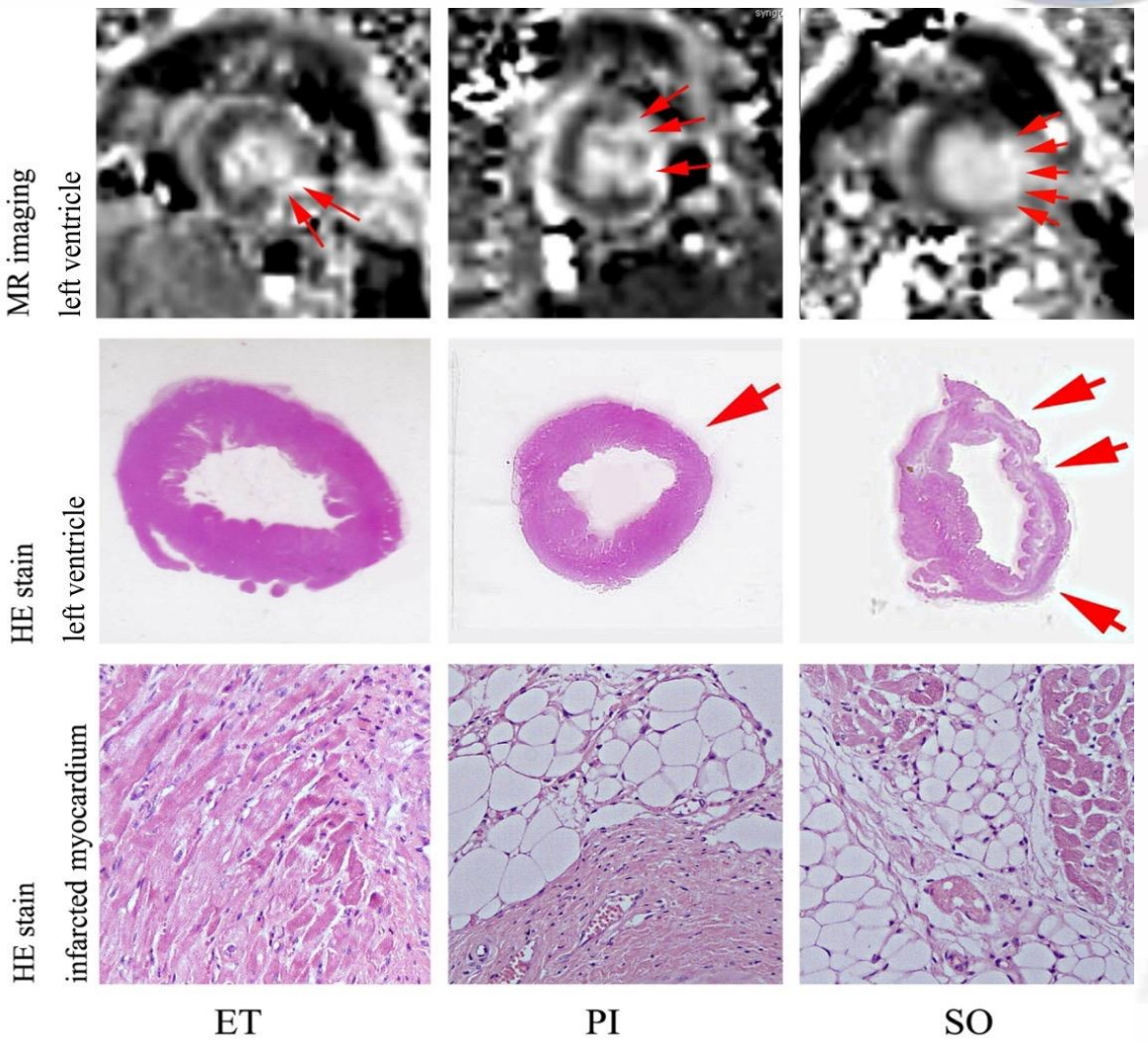
Reduced Size of myocardial infarction protected by PIT

ET: remote ischemic training

PI: Pure ischemia

SO: sham operation

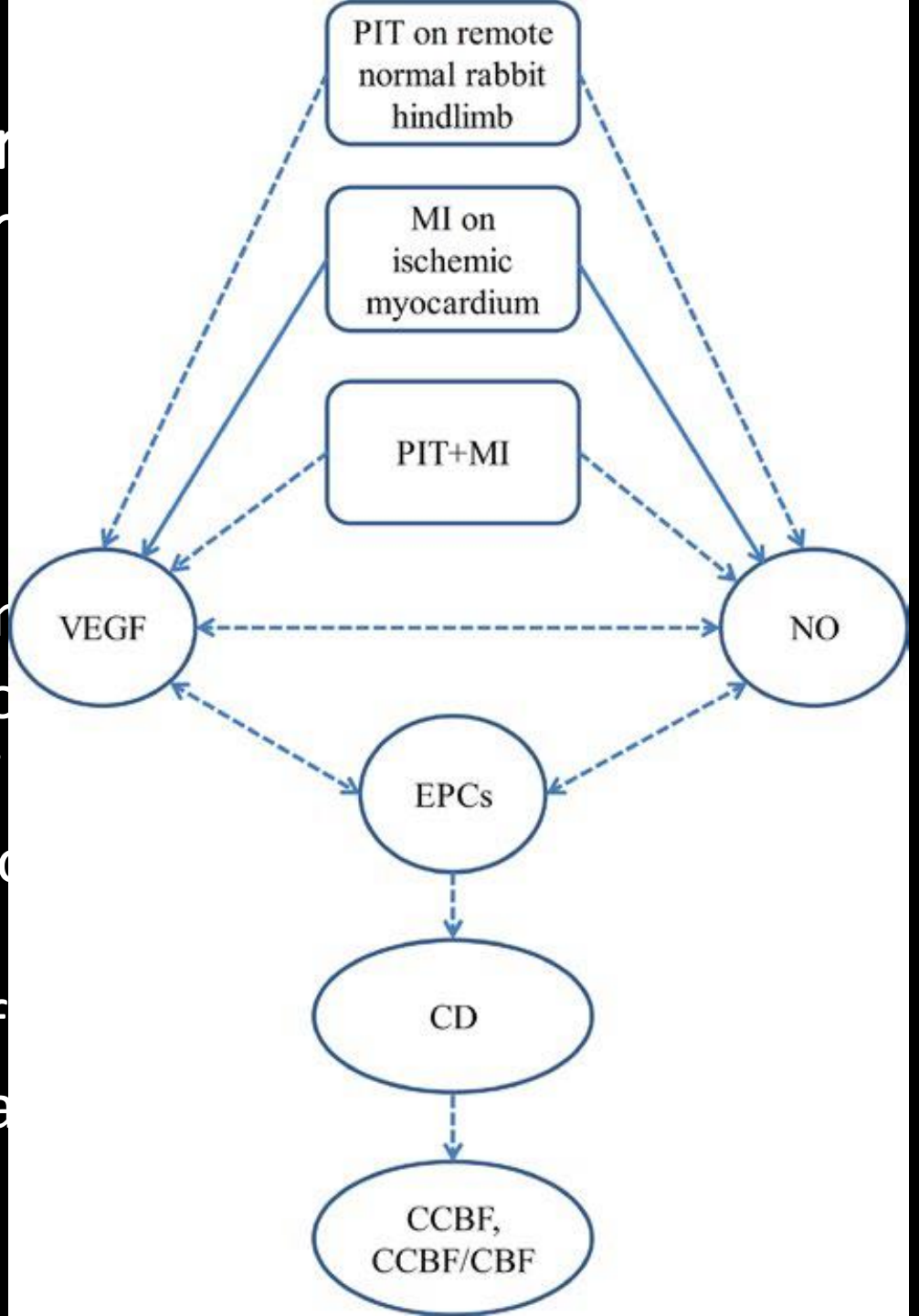


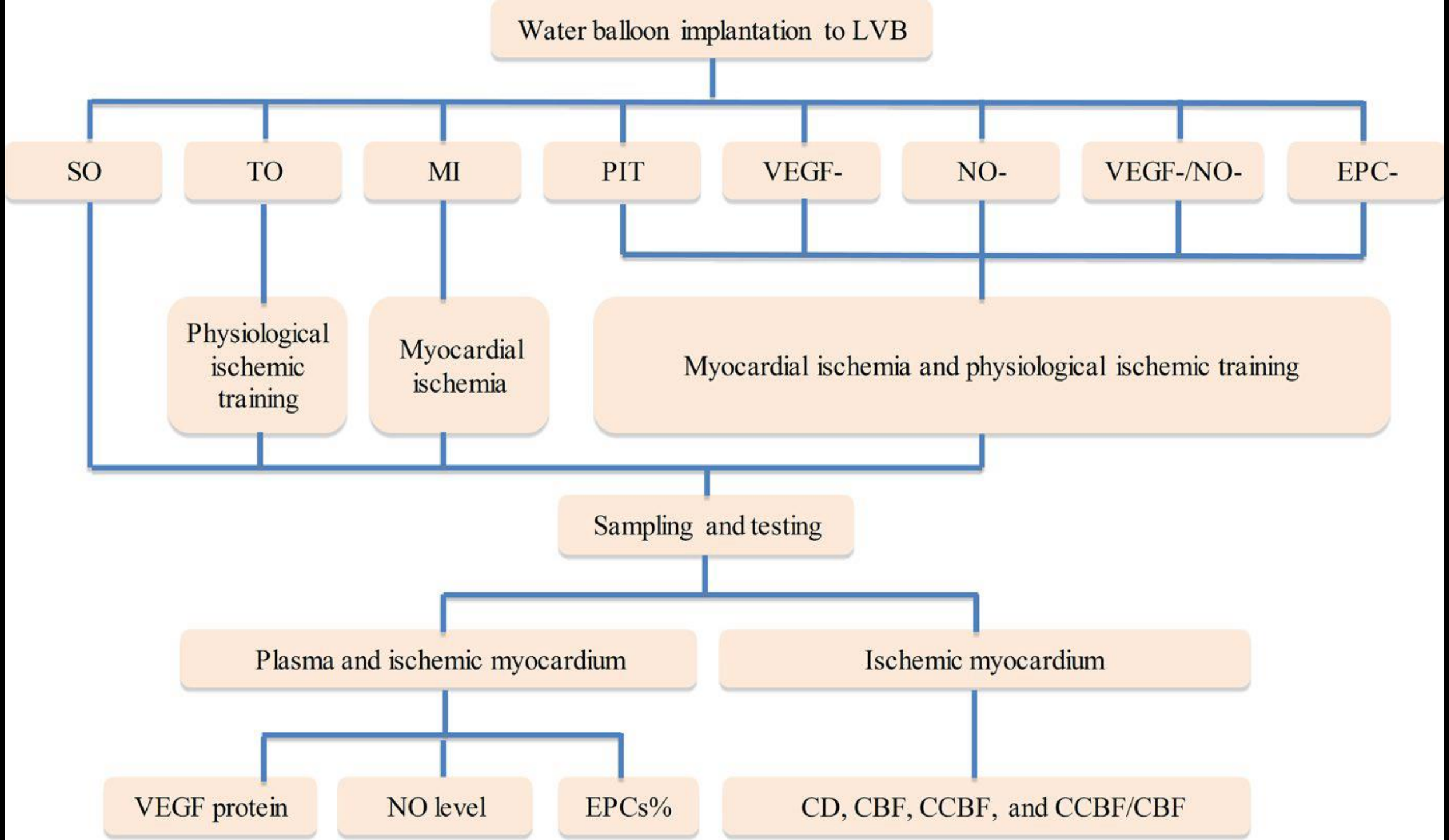


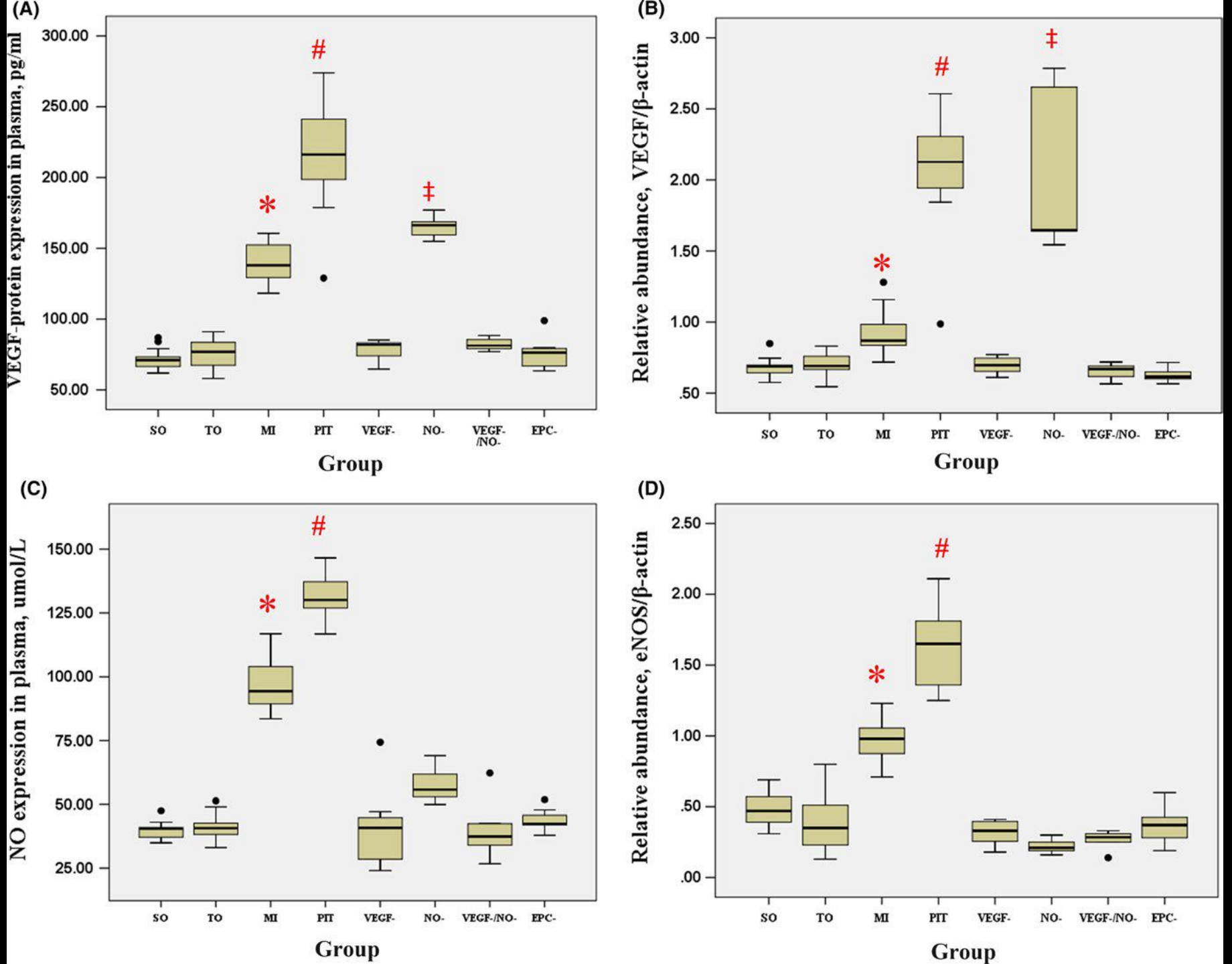
Remote physiological ischemic training pr
angiogenesis via molecular and cellular m
myocardial ischemia

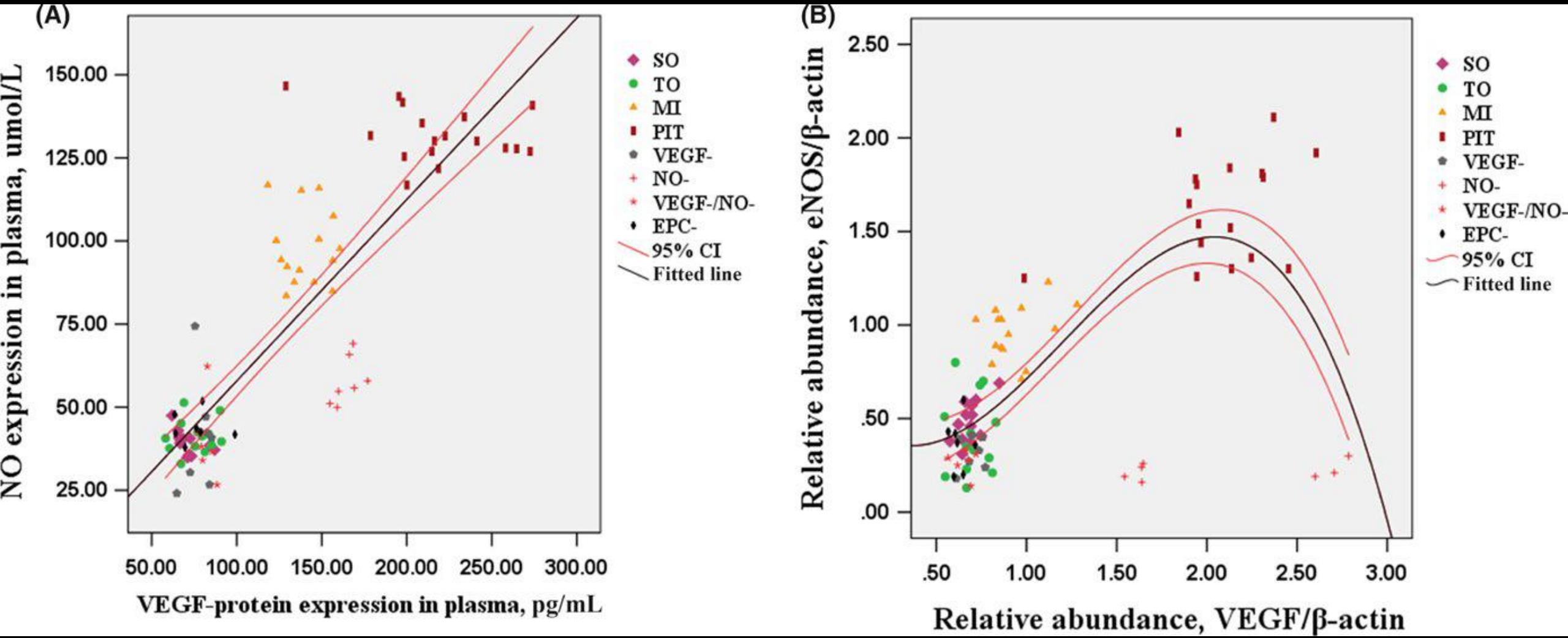
- Zheng Y, et al. Cardiovasc Ther. 2017 Jun;35(3)

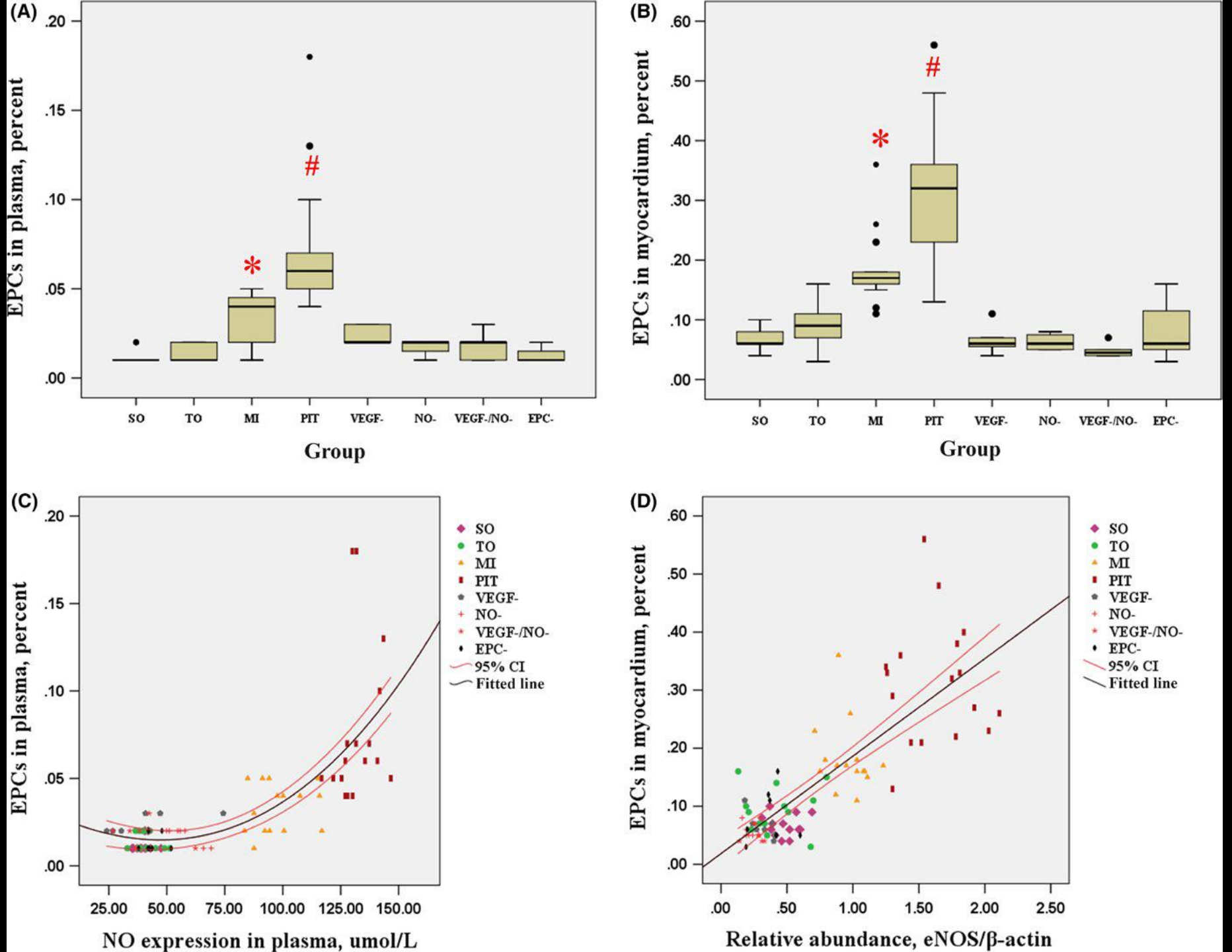
- Myocardial ischemia (MI) rabbit models by cor
around the left ventricular branch to induce co
- The PIT procedure consisted of three cycles of
inflation on the hind limbs with a reperfusion
and myocardial EPC numbers, VEGF level, and
well as capillary density (CD), coronary blood f
coronary collateral blood flow (CCBF) in myoca
measured.

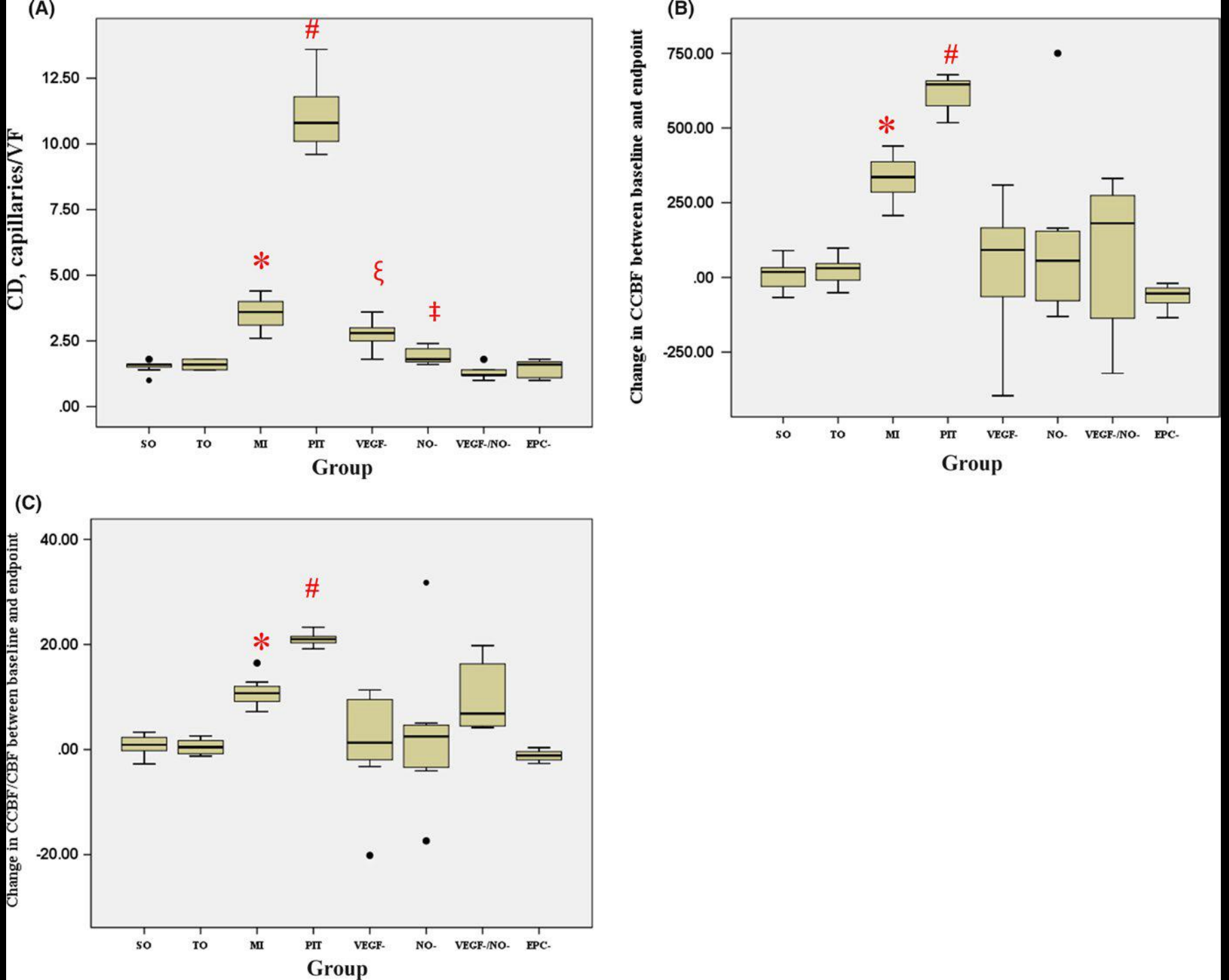


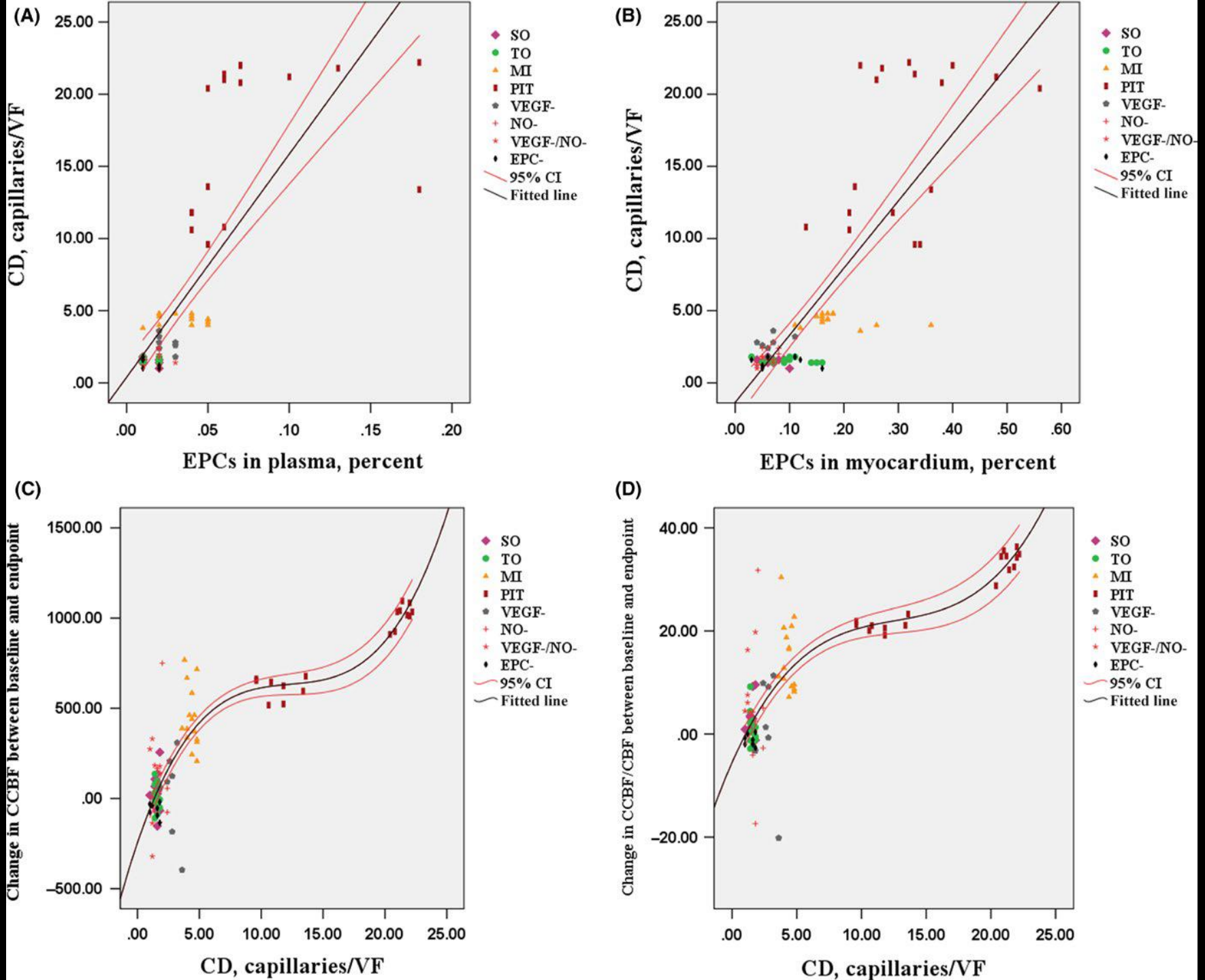

Water balloon implantation to LVB
SO
TO
MI
PIT
VEGF-
NO-
VEGF-/NO-
EPC-
Physiological ischemic training
Myocardial ischemia
Myocardial ischemia and physiological ischemic training
Sampling and testing
Plasma and ischemic myocardium
Ischemic myocardium
VEGF protein
NO level
EPCs%
CD, CBF, CCBF, and CCBF/CBF


(A)
VEGF-protein expression in plasma, pg/ml
300.00
250.00
200.00
150.00
100.00
50.00
SO
TO
MI
PIT
VEGF-
NO-
VEGF-/NO-
EPC-
Group
(B)
Relative abundance, VEGF/β-actin
3.00
2.50
2.00
1.50
1.00
.50
Group
(C)
NO expression in plasma, umol/L
150.00
125.00
100.00
75.00
50.00
25.00
Group
(D)
Relative abundance, eNOS/β-actin
2.50
2.00
1.50
1.00
.50
.00
Group


(A)
NO expression in plasma, umol/L
150.00
125.00
100.00
75.00
50.00
25.00
50.00
100.00
150.00
200.00
250.00
300.00
VEGF-protein expression in plasma, pg/mL
SO
TO
MI
PIT
VEGF-
NO-
VEGF-/NO-
EPC-
95% CI
Fitted line
(B)
Relative abundance, eNOS/β-actin
2.50
2.00
1.50
1.00
.50
.00
.50
1.00
1.50
2.00
2.50
3.00
Relative abundance, VEGF/β-actin
SO
TO
MI
PIT
VEGF-
NO-
VEGF-/NO-
EPC-
95% CI
Fitted line


(A)
EPCs in plasma, percent
.20
.15
.10
.05
.00
*
#
SO
TO
MI
PIT
VEGF-
NO-
VEGF-/NO-
EPC-
Group
(B)
EPCs in myocardium, percent
.60
.50
.40
.30
.20
.10
.00
*
#
SO
TO
MI
PIT
VEGF-
NO-
VEGF-/NO-
EPC-
Group
(C)
EPCs in plasma, percent
.20
.15
.10
.05
.00
25.00
50.00
75.00
100.00
125.00
150.00
NO expression in plasma, umol/L
SO
TO
MI
PIT
VEGF-
NO-
VEGF-/NO-
EPC-
95% CI
Fitted line
(D)
EPCs in myocardium, percent
.60
.50
.40
.30
.20
.10
.00
.00
.50
1.00
1.50
2.00
2.50
Relative abundance, eNOS/β-actin
SO
TO
MI
PIT
VEGF-
NO-
VEGF-/NO-
EPC-
95% CI
Fitted line


(A)
CD, capillaries/VF
12.50
10.00
7.50
5.00
2.50
.00
#
*
ξ
‡
SO
TO
MI
PIT
VEGF-
NO-
VEGF-/NO-
EPC-
Group
(B)
Change in CCBF between baseline and endpoint
750.00
500.00
250.00
.00
-250.00
#
*
SO
TO
MI
PIT
VEGF-
NO-
VEGF-/NO-
EPC-
Group
(C)
Change in CCBF/CBF between baseline and endpoint
40.00
20.00
.00
-20.00
#
*
SO
TO
MI
PIT
VEGF-
NO-
VEGF-/NO-
EPC-
Group


(A)
CD, capillaries/VF
25.00
20.00
15.00
10.00
5.00
.00
.00
.05
.10
.15
.20
EPCs in plasma, percent
SO
TO
MI
PIT
VEGF-
NO-
VEGF-/NO-
EPC-
95% CI
Fitted line
(B)
CD, capillaries/VF
25.00
20.00
15.00
10.00
5.00
.00
.00
.10
.20
.30
.40
.50
.60
EPCs in myocardium, percent
SO
TO
MI
PIT
VEGF-
NO-
VEGF-/NO-
EPC-
95% CI
Fitted line
(C)
Change in CCBF between baseline and endpoint
1500.00
1000.00
500.00
.00
–500.00
.00
5.00
10.00
15.00
20.00
25.00
CD, capillaries/VF
SO
TO
MI
PIT
VEGF-
NO-
VEGF-/NO-
EPC-
95% CI
Fitted line
(D)
Change in CCBF/CBF between baseline and endpoint
40.00
20.00
.00
–20.00
.00
5.00
10.00
15.00
20.00
25.00
CD, capillaries/VF
SO
TO
MI
PIT
VEGF-
NO-
VEGF-/NO-
EPC-
95% CI
Fitted line

Conclusion

- This study shows that PIT promotes revascularization, through upregulating VEGF expression, thus NO level, and finally the mobilization of EPCs.
- Findings in the current study may also broaden the knowledge regarding the function of VEGF in the regulation of NO synthesis under PIT. As compared to the surgical treatment, this specific alternative method may be able to noninvasively improve the function of cardiovascular system, activity of daily living, and quality of life in patients with cardiovascular ischemic diseases.

Recent publications

- Zheng Y, et al. Remote physiological ischemic training promotes coronary angiogenesis via molecular and cellular mobilization after myocardial ischemia. Cardiovasc Ther 2017 Jun;35(3)
- Wan C, **Li J**, Bi S, Zhao Y, Lin A, Dynamics of Endogenous Endothe lial Progenitor Cells Homing Modulated by Physiological IschAemia Training,J Rehabil Med 2015; 47: 87–93
- Xiao M, Lu X, **Li J**, Li L, &Li Y. Physiologic ischaemic training induces endothelial progenitor cell mobilization and myocardial angiogenesis via endothelial nitric oxide synthase related pathway in rabbits. Journal of Cardiovascular Medicine,15(4): 280-287,2014.
- Lin, S.Chen, Y.Li, Y.**Li, J**. Lu, X. "Physical ischaemia induced by isometric exercise facilitated collateral development in the remote ischaemic myocardium of humans." Clin Sci (Lond) 127(10): 581-588. 2014
- Wan C, **Li J**, Yang C, Hu D, &Bi S. Dynamics of endogenous endothelial progenitor cells homing modulated by physiological ischemia training. Journal of Rehabilitation
- Zheng Y, Lu X, **Li J**, Zhang Q&Reinhardt JD.Impact of remote physiological ischemic training on vascular endothelial growth factor, endothelial progenitor cells and coronary angiogenesis after myocardial ischemia. International Journal of Cardiology, 177(3):894-901, 2014.
- Lin S, Lu X, Chen S, Ye F, Zhang J, Ma Y, & **Li J**. Human coronary collateral recruitment is facilitated by isometric exercise during acute coronary occlusion. Journal of Rehabilitation Medicine, 44: 691-695, 2012.

- Gao J, Shen M, & **Li J**. Proteome foundation in myocardial collateral formation evoked by the intermittent ischemic training in skeletal muscle in a myocardial ischemia model of rabbit. Cardiovascular Therapeutics, 29: 199-210, 2011.
- Lin A, **Li J**, Zhao Y, Xiao M, Xiao B, Lu X, & Wan C. Effect of Physiologic Ischemic Training on Protection of Myocardial Infarction in rabbits. American Journal of Physical Medicine and Rehabilitation, 90: 97-105, 2011.
- Wan C, **Li J**, & Yi L. Enhancement of Homing Capability of Endothelial Progenitor Cells to Ischaemic Myocardium Through Physiological Ischaemia Training. Journal of Rehabilitation Medicine, 43: 550-555, 2011
- Zhao Y, **Li J**, Lin A, Xiao M, Xiao B, & Wan C. Improving angiogenesis and muscle performance in the ischemic limb model by physiological ischemic training in rabbits. American Journal of Physical Medicine and Rehabilitation, 90: 1020-1029, 2011.
- Gu J, Wang Y, **Li J**, Wang J, & Jin T. Proteomic Analysis of Left Ventricular Tissues following Intermittent Myocardial Ischemia during Coronary Collateralization in Rabbits. International Journal of Cardiology, 131: 326-335, 2009.
- Shen M, Gao J, **Li J**, & Su J. Effect of stimulation of frequency on angiogenesis and gene expression in ischemic skeletal muscle of rabbit. Canadian Journal of Physiology and Pharmacology, 87: 396-401, 2009.
- Shen M, Gao J, **Li J**, & Su J. Effect of ischemic exercise training of normal limb on angiogenesis of pathological ischemic limb in rabbit. Clinical Science, 117: 201-208, 2009.
- Lu X, Wu T, Huang P, Lin S, Qiu F, Meng X, Gao J, & **Li J**. Effect and Mechanism of Intermittent Myocardial Ischemia Induced by Exercise on Collateral Formation. American Journal of Physical Medicine and Rehabilitation, 10: 803-814, 2008.