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

Ischemia

Opening of original collaterals

Increase of shear force on vessels

Remodeling of vascular wall

Formation of functional artery

Endothelial cell

VEGF expression

Angiogenesis

Collateral formation
Study clue: Ischemic preconditioning

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

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

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

Following studies confirmed this remote phenomenon of transient ischemic preconditioning by limb in 2002.
Remote Ischemic preconditioning or training?
Remote Ischemic Preconditioning: Making the Brain More Tolerant, Safely and Inexpensively

Michael A. Moskowitz and Christian Waeber
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
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
Safety-remote preconditioning
Safety-remote preconditioning
Safety-remote preconditioning

LMCA of Healthy volunteers

Stenotic MCA of Patients

RMCA of Healthy volunteers

Normal MCA of Patients

No influence on brain blood flow
Effectiveness in patients with stroke

Upper limb ischemic preconditioning prevents recurrent stroke in intracranial arterial stenosis

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

103 patients assessed for eligibility and randomized as follows:

- **Control group** (52 cases)
- **BAIPC group** (51 cases)

Excluded 22 cases:
- 11 cases refused follow-up with SPECT.
- 7 cases underwent stent placement after 2-3 weeks of treatment (no new stroke onset; >90% stenosis).
- 4 cases with incomplete data.

Excluded 13 cases:
- 4 cases refused follow-up with SPECT.
- 4 cases underwent stent placement after 2-3 weeks of treatment (no new stroke onset; >90% stenosis).
- 5 cases with incomplete data.

- 30 completed study, 30 analyzed
- 38 completed study, 38 analyzed
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.
Preconditioning reaches clinical practice in intracranial arterial stenosis

Brad E. Zacharia, MD
Samuel S. Bruce, BA
Turgut Tadrisunak, MD, PhD

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. 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. 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
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.

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

**VEGF**

**GAPDH**

**MI**

**MI-HE**

**MI-N**

**MI-S**

★

★

★

★★

★★

★★★

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

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

RIT: remote ischemic training
MI: Pure ischemia
Sham: sham operation
Reduced Size of myocardial infarction protected by PIT

ET: remote ischemic training
PI: Pure ischemia
SO: sham operation
Remote physiological ischemic training promotes coronary angiogenesis via molecular and cellular mobilization after myocardial ischemia


- Myocardial ischemia (MI) rabbit models by constrictor implanted around the left ventricular branch to induce controlled MI.

- The PIT procedure consisted of three cycles of cuff inflation on the hind limbs with a reperfusion of 5 minutes. Plasma and myocardial EPC numbers, VEGF level, and NO concentration, as well as capillary density (CD), coronary blood flow (CBF), and coronary collateral blood flow (CCBF) in myocardium, were measured.
Water balloon implantation to LVB

- SO
- TO
- MI
- PIT
- VEGF-
- NO-
- VEGF-/NO-
- EPC-

1. Physiological ischemic training
2. Myocardial ischemia

**Myocardial ischemia and physiological ischemic training**

- Sampling and testing

  - Plasma and ischemic myocardium
    - VEGF protein
    - NO level
    - EPCs%
  - Ischemic myocardium
    - CD, CBF, CCBF, and CCBF/CBF
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


• 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


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.


