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Peripheral vascular disease as remote ischemic preconditioning, for acute stroke

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ABSTRACT

Objectives: Remote ischemic preconditioning (RIPC) is a powerful endogenous mechanism whereby a brief period of ischemia is capable of protecting remote tissues from subsequent ischemic insult. While this phenomenon has been extensively studied in the heart and brain in animal models, little work has been done to explore the effects of RIPC in human patients with acute cerebral ischemia. This study investigates whether chronic peripheral hypoperfusion, in the form of pre-existing arterial peripheral vascular disease (PVD) that has not been surgically treated, is capable of inducing neuroprotective effects for acute ischemic stroke.
Methods: Individuals with PVD who had not undergone prior surgical treatment were identified from a registry of stroke patients. A control group within the same database was identified by matching patient's demographics and risk factors. The two groups were compared in terms of outcome by NIH Stroke Scale (NIHSS), modified Rankin scale (mRS), mortality, and volume of infarcted tissue at presentation and at discharge.
Results: The matching algorithm identified 26 pairs of PVD-control patients (9 pairs were female and 17 pairs were male). Age range was 20–93 years (mean 73). The PVD group was found to have significantly lower NIHSS scores at admission (NIHSS ≤ 4: PVD 47.1%, control 4.35%, $p < 0.003$), significantly more favorable outcomes at discharge (mRS ≤ 2: PVD 30.8%, control 3.84%, $p < 0.012$), and a significantly lower mortality rate (PVD 26.9%, control 57.7%, $p = 0.024$). Mean acute stroke volume at admission and at discharge were significantly lower for the PVD group (admission: PVD 39.6 mL, control 148.3 mL, $p < 0.005$ and discharge: PVD 111.7 mL, control 275 mL, $p < 0.001$).
Conclusion: Chronic limb hypoperfusion induced by PVD can potentially produce a neuroprotective effect in acute ischemic stroke. This effect resembles the neuroprotection induced by RIPC in preclinical models.

1. Introduction

Ischemic stroke is a leading cause of disability worldwide and the fourth leading cause of mortality in adults [1,2]. There is a growing volume of literature that has demonstrated the powerful effect of ischemic preconditioning as an endogenous neuroprotective mechanism against the effects of cerebral ischemia both in animal models and in early clinical studies [3–7]. However, clinical application of ischemic preconditioning techniques for acute ischemic stroke can be difficult due to the sudden and largely unpredictable nature of acute cerebral ischemia.

Ischemic preconditioning has typically been elicited in both experimental and clinical studies by brief periods of transient, complete ischemia (total suppression of blood flow) to an organ or tissue for a sub-lethal period of time. It has not been previously investigated in a clinical setting whether chronic remote hypoperfusion is as effective at initiating these neuroprotective effects. To address this question, we hypothesized that a pre-existing condition that causes non-cerebral hypoperfusion would have a protective effect in those patients who subsequently suffer a

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Table 1
The NIHSS score ranges that were used to classify each patient.

NIH stroke score ranges	
Normal/near normal examination	0
Minor stroke	1–4
Moderate stroke	5–15
Moderate/severe stroke	16–20
Severe stroke	>20

cerebral infarction. Peripheral vascular disease (PVD) represents just such a condition. We evaluated whether PVD produces a neuroprotective effect, as measured by clinical outcome and infarct volume, by comparing acute ischemic stroke patients with pre-existing, untreated PVD with matched controls with no prior history of PVD.

2. Materials and methods

2.1. Patient selection

Patients with a history of PVD were retrospectively identified from a prospectively collected institutional registry of acute ischemic stroke cases. Only individuals who had not undergone any prior surgical intervention for PVD were included. For each PVD patient, a control was identified using a risk-factor matching algorithm. This algorithm matched patients demographically based on age, sex, ethnicity, and race, followed by past medical history for at least two of the following conditions: hypertension, diabetes mellitus, or tobacco use, stroke and transient ischemic attacks (TIA).

2.2. Clinical measurements

NIH stroke scale (NIHSS) at presentation and functional outcome at discharge as indicated by modified Rankin scale (mRS) was collected as clinical measurements of stroke severity and clinical outcome. The NIHSS scores were stratified into categories for comparison between groups, as described in Table 1 [8], and the mRS were graded as favorable (mRS 0-2) or unfavorable (mRS 3-6).

2.3. Infarct volume

As an objective measurement of stroke magnitude, the acute stroke volume was measured at presentation and discharge. Acute stroke volume at presentation was evaluated with diffusion-weighted MRI (DWI). Acute ischemic lesions were identified as hyperintense regions consistent with restricted diffusion on $b = 1000\ s/mm^2$ DWIs upon initial hospital admission.

T2-weighted or fluid attenuated inversion recovery (FLAIR) imaging and non-contrast CT were used to determine final stroke volume at time of discharge [10,11]. Final stroke lesion volume was defined as hyperintense regions on FLAIR images or hypodense areas on CT.

Lesion volumes were calculated with the freely available Analysis of Functional NeuroImages software package (AFNI; afni.nimh.nih.gov/afni) using a semi-automated process consisting of manually defining the relative region of the lesion, then thresholding the CT, DWI or FLAIR images based on an empirical intensity-based threshold, and manually editing the resulting contours to exclude obvious errors. Lesion volumes were estimated by multiplying the voxel resolution by the number of voxels retained within the individual contours.

Table 2
Summary of the demographic and risk factors.

Demographics and risk factors	PVD group	Control group	*p*-Value
Number of patients	26	26	
Mean age ±	73 ± 13.6	73 ± 12.3	
Gender			
Female	9 (34.6%)	9 (34.6%)	
Male	17 (65.4%)	17 (65.4%)	
Ethnicity			
White	21(80.7%)	21(80.7%)	
Black	3 (11.5%)	3 (11.5%)	
Asian	1 (3.9%)	1 (3.9%)	
Unspecified	1 (3.9%)	1 (3.9%)	
Past medical history			
Hypertension	23 (88.5%)	11 (42.3%)	0.001
Diabetes	11 (42.3%)	22 (84.6%)	0.003
Previous stroke	8 (30.8%)	6 (23.1%)	0.755
Previous TIA	3 (11.5%)	2 (7.7%)	1.000
Smoker	3 (11.5%)	2 (7.7%)	1.000
Atrial fibrilation	10 (38.5%)	8 (30.8%)	0.771

2.4. Statistics

Categorical variables, including stratified NIHSS and mRS, were compared between groups using the Fisher Exact Test for 2×2 contingency tables. The mortality rates between the two groups were compared using an odds ratio. Imaging stroke volumes were compared using a paired *t*-test. Statistical analysis was performed using R: A Language and Environment for Statistical Computing, version 2.15.1 (2012-06-22).

3. Results

3.1. Patient selection

The matching algorithm identified 26 pairs of PVD-control patients. Of these, 9 pairs were female and 17 pairs were male (34.6% and 65.4%). The age range was 20–93 years of age with a mean of 73 years for both groups and comparable standard deviations (PVD 13.6 years, control 12.3 years). The mean age difference between each case and their matched control was 2.5 years. In addition to the clinical risk factors considered in the matching algorithm, the history of atrial fibrillation was compared between the two groups, and found to be no significantly different (38.5% of PVD patients and 30.8% of controls, *p*-value > 0.75). Table 2 details the demographics and risk factors after the matching algorithm was applied.

3.2. Clinical measurements

As a clinical measure of stroke severity, twenty PVD-control pairs had NIHSS scores recorded during their acute hospitalization. The distribution of scores is detailed in Fig. 1. Among patients with PVD, there were a greater number with minor neurological deficits at presentation (NIHSS 1–4) than in control patients (47.1%

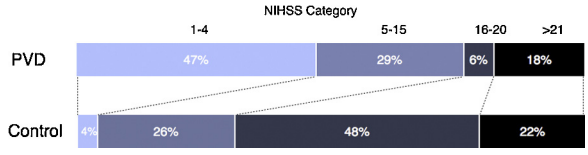

Fig. 1. The distribution of NIHSS score categories between untreated PVD and control patients.