PERFUSION ABNORMALITIES AND CARDIOVASCULAR COMORBIDITIES IN NEUROLOGICAL DISORDERS.

Niels Bergsland[1], Dejan Jakimovski[1], Robert Zivadinov[1,2]

[1]Buffalo Neuroimaging Analysis Center, Department of Neurology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, Buffalo, NY, USA;
[2]Center for Biomedical Imaging at Clinical Translational Science Institute, University at Buffalo, State University of New York, Buffalo, NY, USA

Jacobs School of Medicine and Biomedical Sciences
University at Buffalo

BNAC
Buffalo Neuroimaging Analysis Center

Center for Biomedical Imaging at Clinical and Translational Science Institute

BUFFALO Clinical and Translational RESEARCH CENTER

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Study Disclosures

None

Financial Relationships/Potential Conflicts of Interest

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Background

- The exact etiology of many neurological disorders remains unknown.
- An increased prevalence of cardiac disease has been frequently reported.
- Cardiac disease can have a downstream impact on brain perfusion.
- Local hypoxia stemming from impaired cerebral perfusion may promote the accumulation of lesions or protein aggregates.
- Targeting cardiovascular disease may offer the possibility to aid in the treatment of neurological disorders.

Perfusion imaging with MRI

- Perfusion is the process of delivery of blood to a capillary bed in tissue
- MRI techniques allow for the assessment of tissue perfusion in vivo
- Dynamic susceptibility contrast (DSC) requires the injection of a contrast agent which induces a change in the magnetic susceptibility of the blood
  - Change in MRI signal is continually measured during the passage of the bolus
  - Measurements are typically relative
- Arterial spin labelling (ASL) magnetically "tags" the blood before entering the brain
  - Amount of labelling is then measured and compared to a control region obtained without spin labelling
  - Measurements are truly quantitative

Perfusion basics

- Standard metrics include:
  - Cerebral blood volume (CBV)
    - A measure of the volume as a percentage of the total tissue volume
  - Cerebral blood flow (CBF)
    - The volume of blood per unit time (ml/100 g/min)
  - Mean transit time (MTT)
    - The average time it takes a particle to traverse the vasculature (= CBV/CBF)
  - Time to peak (TTP)
    - The time from contrast arrival to peak in capillary concentration

Perfusion findings in multiple sclerosis

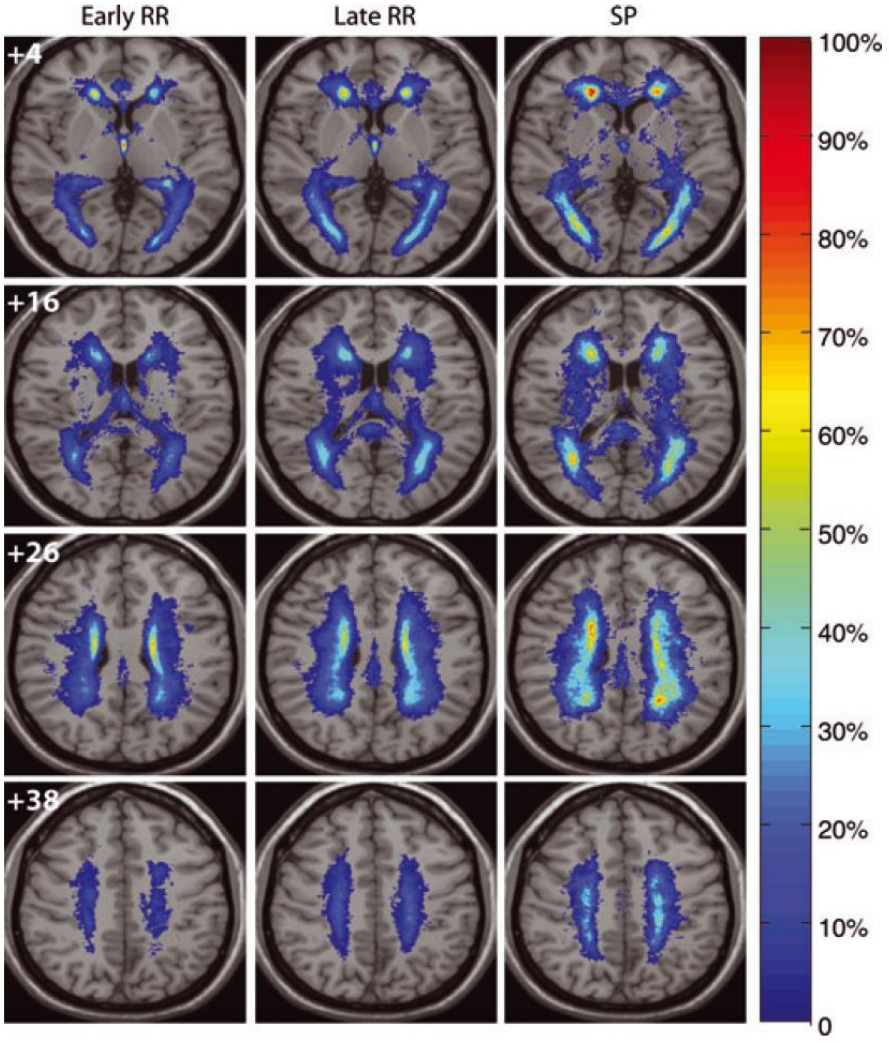
The Relationship between Normal Cerebral Perfusion Patterns and White Matter Lesion Distribution in 1,249 Patients with Multiple Sclerosis

Christopher M. Holland, MD, PhD, Arnaud Charil, PhD, Istvan Csapo, MS, Zsuzsanna Liptak, MD, Masanori Ichise, MD, Samia J. Khoury, MD, Rohit Bakshi, MD, Howard L. Weiner, MD, Charles R.G. Guttmann, MD

- 1249 MS patients (Early/late RR, SP)
- Lesion probability maps compared using an atlas of healthy individuals having undergone SPECT perfusion.

Holland CM, et al. J Neuroimaging. 2012 Apr;22(2):129-36.

Perfusion findings in multiple sclerosis



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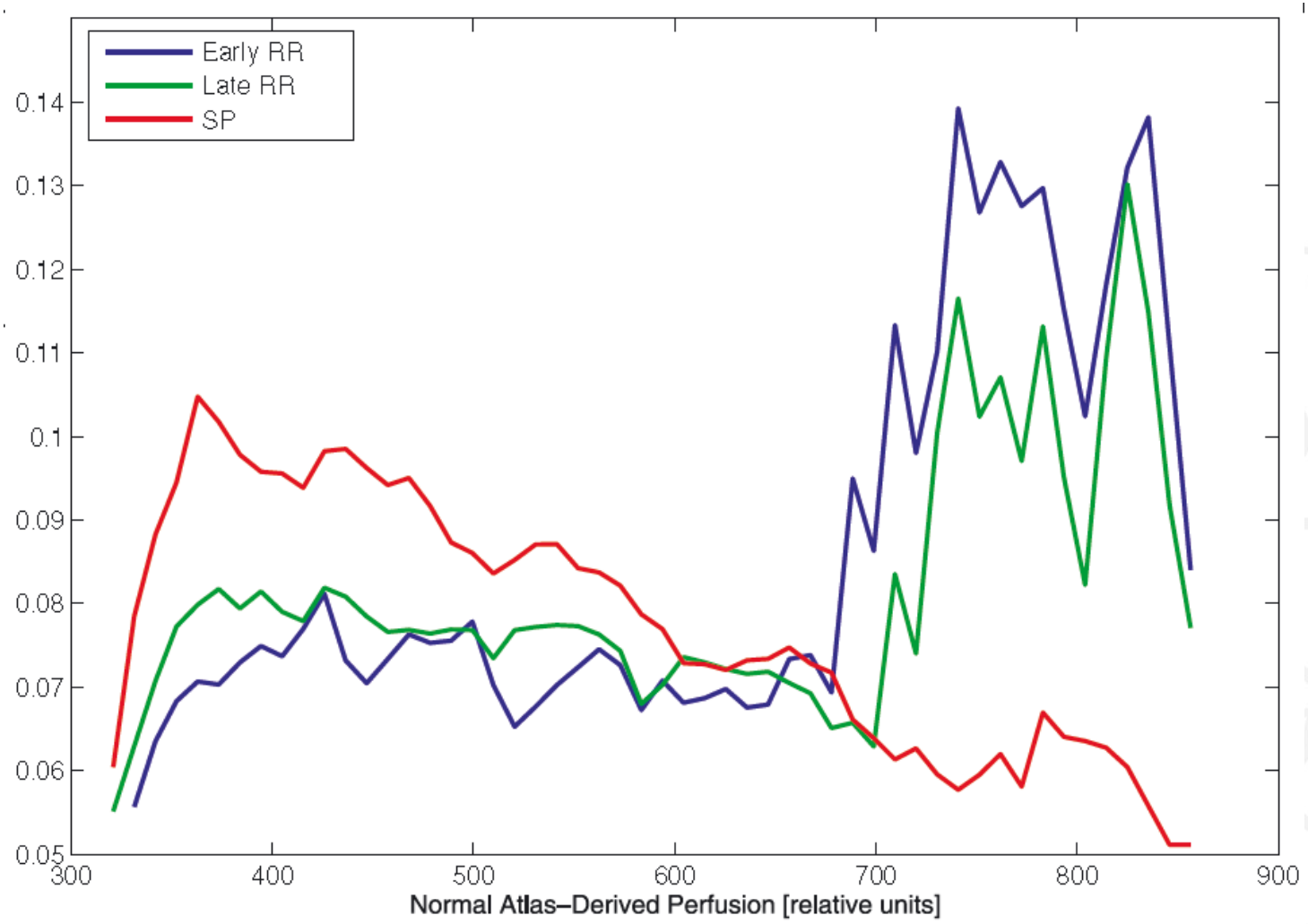
- 1249 MS patients (Early/late RR, SP)
- Lesion probability maps compared using an atlas of healthy individuals having undergone SPECT perfusion
- Lesions were present in areas of relatively lower perfusions compared to normal appearing areas.
- Lesions in SP MS were more common in areas of lower perfusion.

Holland CM, et al. J Neuroimaging. 2012 Apr;22(2):129-36.

Perfusion findings in multiple sclerosis



Holland CM, et al. J Neuroimaging. 2012 Apr;22(2):129-36.

Perfusion findings in Parkinson's disease

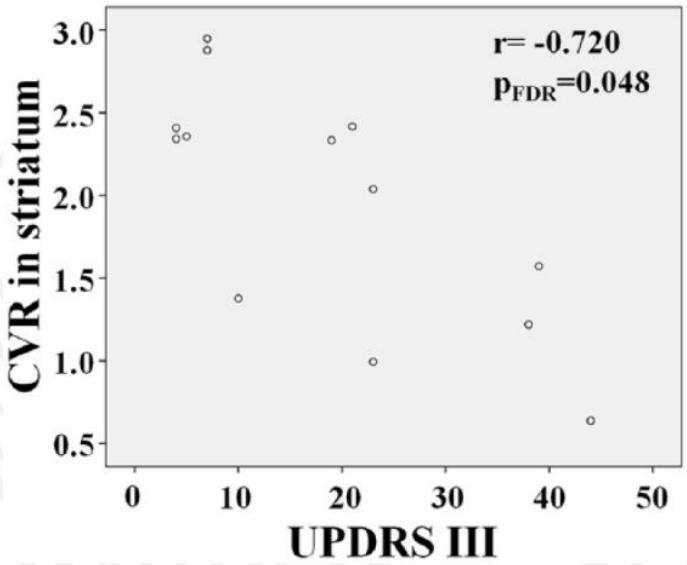
Therapeutic Advances in Neurological Disorders *Original Article*

Cerebral blood flow and cerebrovascular reactivity correlate with severity of motor symptoms in Parkinson's disease

Ther Adv Neurol Disord
2019, Vol. 12: 1–10
DOI: 10.1177/1756286419838354

Laura Pelizzari, Maria Marcella Laganà, Federica Rossetto, Niels Bergsland, Mirco Galli, Giuseppe Baselli, Mario Clerici, Raffaello Nemni and Francesca Baglio

- Inverse relationship between striatal cerebrovascular reactivity (CVR) and UPDRS III scores



Perfusion findings in Alzheimer's disease

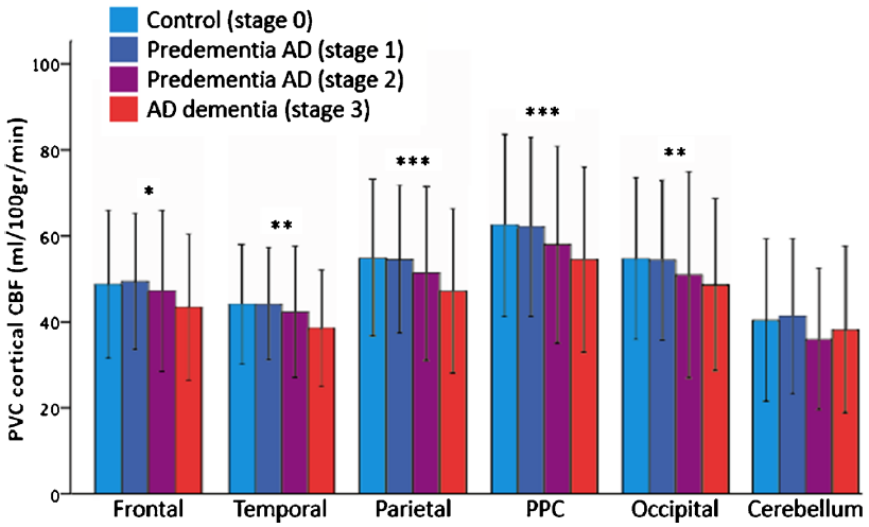
Eur Radiol
DOI 10.1007/s00330-015-3834-9

NEURO

Cerebral perfusion in the predementia stages of Alzheimer's disease

Maja A. A. Binnewijzend[1] · Marije R. Benedictus[2] · Joost P. A. Kuijer[3] · Wiesje M. van der Flier[2,4] · Charlotte E. Teunissen[5] · Niels D. Prins[2] · Mike P. Wattjes[1] · Bart N.M. van Berckel[1] · Philip Scheltens[2] · Frederik Barkhof[1]

- Decreasing CBF was related to more advanced AD in all suptratentorial regions



Binnewijzend MA et al. Eur Radiol. 2016 Feb;26(2):506-14.

Cardiovascular comorbidities in neurological disorders

- Multiple sclerosis (MS)
  - Before diagnosis, significantly decreased cerebrovascular comorbidity and numerically, but significantly, lower cardiovascular comorbidity.[1]
  - After diagnosis, increased risks of both cerebrovascular and cardiovascular comorbidity.[1,2,3]
  - Greater rates of hypertension, obesity, diabetes, and abnormal lipid profiles in MS patients compared to controls.[4]
- Parkinson's disease (PD)
  - Diabetes[5] and obesity[6] are known risk factors for PD.
  - Onset of hypertension before PD diagnosis is significantly associated with an increased risk of motor stage PD.[7]
  - Cardiac autonomic dysfunction is the most prominent cardiac abnormality.[8]
- Alzheimer's disease (AD)
  - Cardiovascular disease contributes to the pathogenesis of AD.[9]
  - Heart failure patients exhibit progressive cognitive decline, similar to AD. [10]

[1] Thormann A et al. J Neurol. 2016 Dec;263(12):2484-2493.; [2] Jadidi E et al. Mult Scler. 2013 Sep;19(10):1336-40. ; [3] Christiansen CF et al. Neuroepidemiology. 2010;35(4):267-74.; [4] Jakimovski et al. Expert Rev Neurother. 2019 May;19(5):445-458.[5] Driver JA et al. Diabetes Care. 2008 Oct;31(10):2003-5.; [6] Chen et al Am J Epidemiol. 2004;159:547–555.; [7] Hou et al. Front Neurol. 2018; 9: 162.; [8] Scorza FA et al. J Clin Neurosci. 2018 Jul;53:1-5. [9] Alosco et al. Heart Fail Rev. 2015 Sep; 20(5): 561–571. [10] Weintraub S et al. Cold Spring Harb Perspect Med. 2012 Apr; 2(4):a006171.

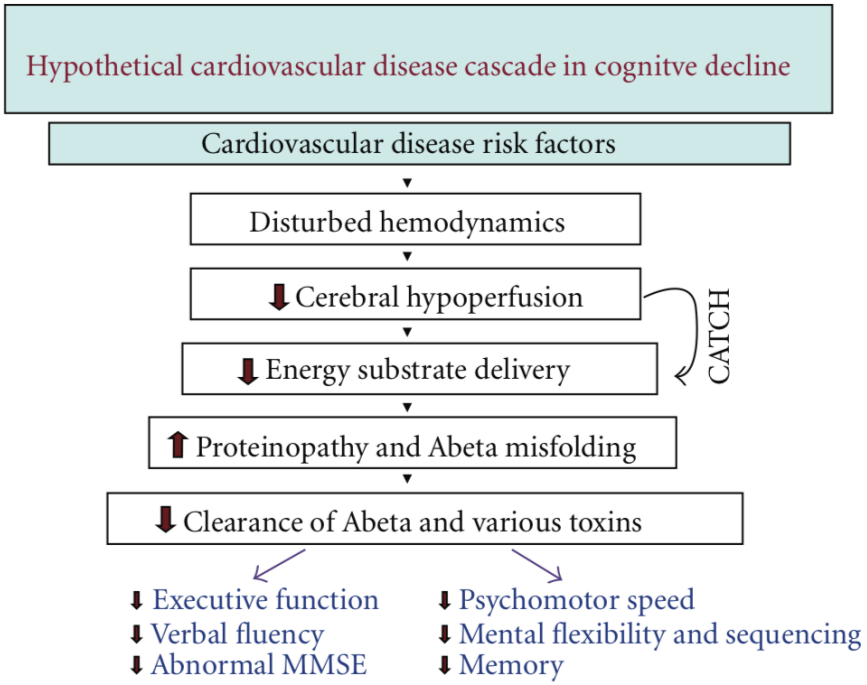
Linking cardiovascular aspects and cerebral perfusion

- Hypertension
  - Damage to endothelial and smooth muscle cells can lead to hypoperfusion.[1]
  - Increased amyloid-beta production may promote vasoconstriction and/or cerebral angiopathy. [2]
  - Increased vascular resistance can lead to reduced blood flow. [3]
- Hypotension
  - May also be associated with cerebral hypoperfusion.[4]
  - Prolonged reaction times compared to normotensives in cognitive testing.[5]
  - Linked to increased risk of Alzheimer's disease and dementia.[4]
- What about cerebral autoregulation?
  - Compensatory cerebral autoregulation does not adequately prevent hypoperfusion.[6]
  - Cerebral autoregulation may become impaired with aging possibly due to atherosclerosis, arterial stiffness, or cardiovascular disease. [6]

[1]O'Rourke MF et al. Hypertension. 2005 Jul;46(1):200-4.; [2] Shah NS et al. Hypertension. 2012 Apr;59(4):780-6. [3] O'Rourke MF et al. J Am Coll Cardiol. 2007 Jul 3;50(1):1-13. [4] de la Torre JC. Ann N Y Acad Sci. 2000;924:136-52. [5] Duschek S et al. Clin Auton Res. 2003 Dec;13(6):427-32. [6] de la Torre JC. Cardiovasc Psychiatry Neurol. 2012;2012:367516

Hypoperfusion as a cause of neuronal energy crisis/injury

- Similar rates of perfusion between the hippocampus and cerebellum. [1]
- Metabolic demand of the hippocampus is considerably greater. [1]
- Decreased hippocampal energy supply may then facilitate neuronal injury.



Legend: CATCH - Critically attained threshold of cerebral hypoperfusion
Figure adapted from [2].

1 Silverman DH et al. Mol Genet Metab. 2001 Sep-Oct;74(1-2):128-38. ; [2] de la Torre JC. Cardiovasc Psychiatry Neurol. 2012;2012:367516.

Thank you! Any questions?