Cerebral perfusion and vascular reactivity in insulin resistance and obesity

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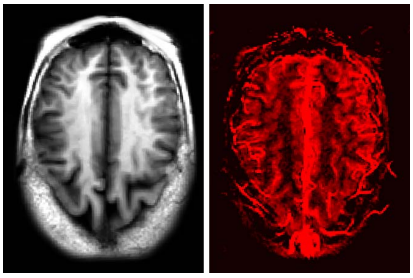
The obesity epidemic is responsible for the increasing prevalence of Type 2 diabetes, with its corresponding micro- and macrovascular comorbidities. Using a high-resolution arterial-spin labeling (ASL) 3T MRI technique, we present evidence that brain perfusion and vascular reactivity (VR) are affected in the early (insulin resistance) stage of this disease.

Methods

82 middle-aged (age range 35-59) volunteers included 35 healthy controls (HC), 24 insulin-resistant non-diabetics (IR), and 23 diabetics (DB). The groups were matched for age and gender, but both IR and DB patients were significantly more obese than the HC group (see table). The insulin resistance index QUICKI was significantly lower for IR than HC, and also lower for DB than IR patients.



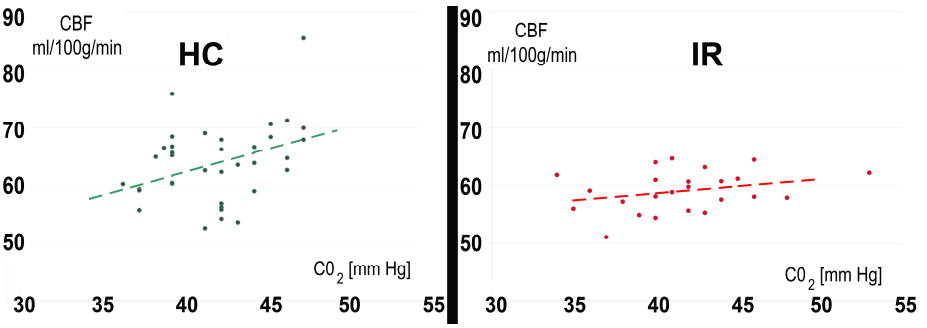
ASL acquisition is based on segmented TrueFISP readout and FAIR preparation. A 12-element head coil receiver and a body coil were used. TrueFISP was implemented as an interleaved acquisition of 3 k-space segments, 53 lines (217.3 ms) per segment, TR/TE = 3.4 / 1.7ms, FA = 50^{O}, 256 x 192 matrix, 1.2 x 1.2 x 8 mm^3 voxels, NEX = 8, 2:10 mins / slice. A general kinetic model [1] and white matter constraints were used for flow calculation. By using 1.2 sec tagging delay and 3T field strength, we achieved high S/N at the cost of confounding signal in large (~1mm diameter) blood vessels. However, contribution from the blood vessels can be readily excluded from tissue flow based on a global threshold. The spatial resolution and tissue contrast resolution of segmented TrueTFISP (figure, left panel) allowed for confident separation of perfusion of cortical gray matter from white matter (right panel). Vascular reactivity, or the capability of the vascular system to increase blood flow in response to increased demand, was measured both cross-sectionally and within subjects, through response to increased CO_2 levels achieved using a rebreathing challenge.

group	BMI		waist/height		QUICKI	
	Avg.	st.dev.	Avg.	st.dev.	Avg.	st.dev.
HC	25.3	5.0	0.54	0.08	0.393	0.030
IR	32.3	7.5	0.62	0.09	0.336	0.026
DB	33.1	4.9	0.66	0.07	0.303	0.039

Results and Discussion

Resting cerebral blood flow (CBF) was fitted well by a linear regression model that included end-tidal CO_2 as the continuous dependent variable and group membership as the categorical variable. There was a significant improvement in fit when we entered the CO_2 * group interaction, with overall residual standard error 5.3 ml/100g/min, F-statistic 5.578, and p-value 0.002. Plots of gray matter perfusion vs end-tidal CO_2 (figures below) supports the notion that as a group, IR subjects (slope = 0.243) and diabetic patients (slope = 0.448) show reduced vascular reactivity as compared with healthy brains (slope = 0.794).

Factor	Coeff.	Std.Err.	t-value	Pr(>|t|)
Intercept	25.11	11.92	2.106	0.040
CO_2	0.90	0.28	3.234	0.002
CO_2 * group	-0.81	0.39	-2.099	0.040
group	31.22	16.41	1.902	0.062



IR subjects also had significantly lower (p=0.008) resting gray matter flow (60.0±4.5) compared to HC (63.6±6.4), with a trend for hypoperfusion in the DB group. There was a highly significant reduction in white matter flow in both the IR and DB group. In the IR patients, white matter hypoperfusion could be directly attributed to obesity. Under CO_2 challenge, each group demonstrated a significant flow increase over the baseline state. Interestingly, within the IR group, there was a significant detrimental effect of obesity (BMI) on vascular reactivity.

Our measurements of the resting cortical CBF in middle-age adults agree well with the cortical CBF distribution previously measured in diabetic patients using PET ^{15}O, the gold standard, and transcranial Doppler [2], a commonly used technique. Interestingly, the variability of our ASL technique (62.4±4.8 for DB group) was several times lower than for PET and Doppler methods, indicating superior precision, required for detection of subtle functional impairments.

The unexpected finding of larger impairment in IR than in DB group may be explained by the beneficial effect of aggressive drug treatment in diabetics. While many details remain unknown, our findings suggest that cerebral blood flow and vascular reactivity changes resulting from obesity and insulin resistance are reversible.

[1] Buxton RB et al. A general kinetic model for quantitative perfusion imaging with ASL. Magn Reson Med 40: 383–396, 1998.
[2] Brundel M et al. Cerebral haemodynamics, cognition and brain volumes in type 2 diabetes. J Diabetes & Complic. 26(3): 205-9, 2012.