Effects of Age and Smoking on Endothelial Function Assessed by Quantitative MRI in the Peripheral and Central Vasculature

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Introduction: Proper endothelial function (EF) entails the arteries' ability to dilate and constrict in response to functional demands. Nitric oxide (NO) is the key signaling molecule responsible for vasodilation, ensuring vascular homeostasis and protection of the endothelium from injury caused by circulating cytokines. Various conditions, including hypertension, hypercholesterolemia, smoking, diabetes mellitus, etc., but also advanced age, result in reduced release of NO either because of impaired synthesis or bioavailability[1], collectively referred to as 'endothelial dysfunction'. Here we measured various surrogates of EF including hyperemia following cuff occlusion via dynamic venous oximetry[2] and arterial hyperemia[3] as well as multi-segment pulse-wave velocity (PWV) from aortic arch to femoral arteries as part of a single MR protocol in young and old smokers and nonsmokers.

Methods: To date, 132 subjects, divided into young healthy non-smokers (YNS; N = 40, age = 30.1±4.4), young smokers (YS; N = 23, 31.8±4.6 years), old healthy non-smokers (ONS; N = 38, 57.8±3.9 years), and old smokers (OS; N = 31, 55.8±4.1 years). None of the subjects had a history of cardiovascular disease. All MRI studies were performed at 3T (Siemens Tim Trio) with extremity and body matrix coils. The quantitative MRI protocol to evaluate central and peripheral vascular reactivity comprised measurement of reactive hyperemia in the leg induced by cuff occlusion (2 mins baseline, 5 mins occlusion and 6 mins recovery). A multi-echo GRE sequence with velocity-encoded projections[3] was launched to measure venous oxygenation (SvO_2) and arterial velocity simultaneously at 1.25s/120msec temporal resolution. During baseline scanning the velocity waveform in the femoral artery[4] and blood oxygen saturation[5,6] in the femoral vein were quantified. During hyperemia, peripheral vascular reactivity was assessed in terms of washout time (time elapsed to observe desaturated blood to pass through the imaging slice), upslope (mean rate of oxygen resaturation) and overshoot (transient maximal above-baseline HbO_2 level)[7], which are derived from the post-ischemic time-course of SvO_2 (**Fig. 1A**). Further, from the time-resolved arterial blood flow velocity, arterial pulsatility index (PI) and pulse ratio (ratio of systolic to diastolic peak-to-peak velocities) at baseline were evaluated, together with the peak-to-baseline flow rate (rQ_{max}) and duration of forward flow (T_{FF}) during hyperemia (**Fig. 1B**). In addition, at baseline, simultaneous excitation with velocity-encoded time-resolved projections for measuring PWVs along the aortic arch (aPWV), thoracoabdominal aorta (daPWV), and iliofemoral arteries (ifPWV) were acquired to assess arterial stiffness. PWV was obtained by monitoring the velocity waveform at two arterial segments yielding the transit time of the pressure pulse based on the foot-to-foot approach[7,8]. One-way analysis of variance (ANOVA) was performed to the previously described quantitative MRI metrics derived with in-house software. Nonparametric Wilcoxon test, corrected for multiple comparisons, was used for post-hoc analysis (JMP 10.0.0 SAS Institute Inc.).

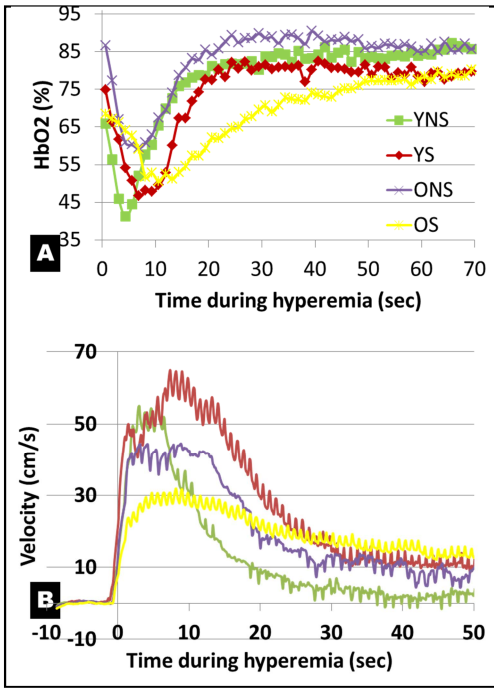

Fig. 1 A: Dynamic venous oximetry (SvO_2) to measure vascular reactivity during hyperemia based on phase images of representative subjects from 4 groups. Older subjects and smokers differ in vascular characteristics from young and non-smokers. B: Projection based dynamic arterial velocimetry for the same subjects during hyperemia averaged over 2-sec sliding window. Consistent reactivity differences in arterial sites were observed in older subjects and smokers.

Table 1. Observed significant differences (P≤0.01) between YNS vs. ONS (aging effect) and YNS vs. YS (smoking effect, red) based on dynamic oximetry, velocimetry, and pulse-wave velocity metrics. The mean and standard deviation values of MRI metrics for each group are listed in the first 4 columns.

Metrics	YNS	YS	ONS	OS	Comparison	P-value
Upslope (%HbO2/s)	3.5±1.5	3.1±1.0	2.6±1.3	2.3±1.2	YNS vs ONS	0.005
Overshoot (%HbO2)	28.6±11.8	19.7±7.5	17.4±9.8	14.2±12.2	YNS vs ONS YNS vs YS	<0.001 0.003
Pulse Ratio	3.1±0.8	3.0±0.6	3.6±0.6	3.3±0.6	YNS vs ONS	0.001
TFF (sec)	36.3±12.1	29.3±9.0	35.4±23.3	30.4±13.0	YNS vs YS	0.008
aPWV (m/s)	7.6±2.2	7.2±1.3	9.0±3.3	9.3±3.0	YNS vs ONS	0.016
daPWV (m/s)	4.6±1.3	4.7±1.4	6.6±2.7	7.3±2.2	YNS vs ONS	<0.001
ifPWV (m/s)	6.2±1.3	6.5±1.7	7.3±1.6	7.6±2.3	YNS vs ONS	0.002

Results: The results of ANOVA indicate that PWVs in all three arterial segments along with upslope and overshoot are significantly different ($p < 0.01$) between the four groups (P≤0.01). Age-related impairment in the vascular reactivity is characterized by lower SvO_2 upslope, overshoot and T_{FF} during hyperemia, as well as decreased baseline arterial pulse ratio, together with elevated baseline PWV in all three segments in old non-smokers compared to young non-smokers (P<0.05, **Table 1**). Overshoot and forward flow period during hyperemia demonstrated a significant smoking-related effect (P<0.01), with lower overshoot and forward flow period in young smokers compared to young non-smokers (**Table 1, red**).

Conclusions: The results indicate that MRI biomarkers of endothelial function are strongly dependent on both age and smoking history. Particularly the peripheral reactivity parameters including overshoot and forward flow time via oximetry and velocimetry as well as PWV reflecting arterial stiffness demonstrated significant differences between groups. Of particular relevance is the observation of impaired endothelial function in young smokers relative to their nonsmoking peers.

References: [1] Cooke et al, Annu Rev Med, 1997; [2] Langham et al, MRM 2010; [3] Langham and Wehrli, JCMR 2011; [4] Celermajer et al, Lancet 1992; [5] Haacke et al, HBM 1997; [6] Fernández-Seara et al, MRM 2006; [7] Langham et al, JCMR 2011; [8] Langham et al, JCMR 2013.

Acknowledgment: NIH RO1 HL109545 and K25 HL111422.