Quantitative MRI Reveals Impaired Endothelial Function and Vascular Reactivity in Cigarette Smokers

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Introduction: The deleterious effects cigarette smoking (CS) on the cardiovascular system are well known. Smokers have greater risk for cardio- and neurovascular events, and epidemiological studies show that long-term CS shortens an individual's lifespan by a decade or more[1]. However, CS affects the vascular system well before symptoms occur in the form of endothelial dysfunction, resulting from the action of reactive oxygen species on the endothelium. One of the hallmarks of endothelial dysfunction (EDF) is the arterial system's inability to dilate and constrict in response to functional demands. Here we developed an integrated quantitative MRI protocol for measuring surrogates of EDF and impaired vascular reactivity in the peripheral and central vascular system and applied it to a cohort of smokers and nonsmokers.

Methods: Surrogate parameters of EDF evaluated included hyperemia following occlusion of the femoral artery and vein at the mid-thigh via dynamic venous oximetry[2] (**Fig. 1**) and arterial velocimetry during reactive hyperemia[3] (**Fig. 2**). Reactive hyperemia in the leg was induced by cuff occlusion (2 mins baseline, 5 mins occlusion and 6 mins recovery). A multi-echo GRE sequence was used to measure venous oxygenation (SvO_2) every 1.25s while phase-contrast projection imaging at 120ms temporal resolution yielded arterial velocity, both at baseline and during hyperemia (**Figs. 1** and **2**) yielding the parameters defined in the Figures. In addition, time-resolved projections were collected for measuring pulse-wave velocity (PWV) along the aortic arch (aPWV), thoraco-abdominal aorta (daPWV), and iliofemoral arteries (ifPWV) were acquired to assess arterial stiffness[4]. The patient cohort was comprised of young and old smokers and nonsmokers (N=169), divided into young healthy non-smokers (YNS; N=45, age=30.2±4.7), young smokers (YS; N=39, 31.2±4.4 years), old non-smokers (ONS; N=45, 57.8±4.0 years), and old smokers (OS; N=40, 56.3±3.8 years), all free of cardiovascular disease and asymptomatic. All MRI studies were performed at 3T (Siemens Tim Trio) with extremity and body matrix coils. Two-way analysis of variance was performed to evaluate intergroup difference and to determine whether age was a covariate. In view of future longitudinal studies to evaluate the effect of smoking duration and smoking cessation we also evaluated repeatability in 20 subjects undergoing the protocol twice within 1-2 months.
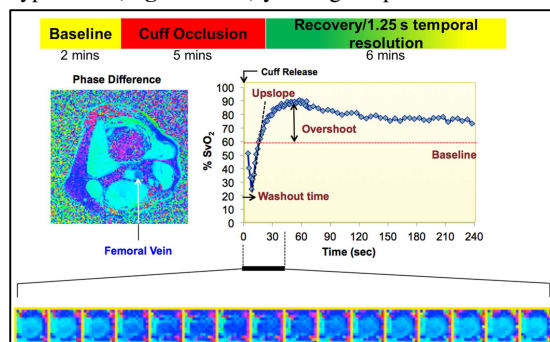

Fig. 1 Time-course of femoral vein SvO_2 during reactive hyperemia yields *Washout Time*, the rate of resaturation (*Upslope*) and rise above baseline (*Overshoot*).
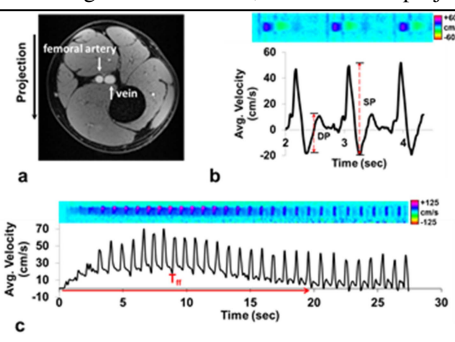

Fig. 2 Femoral artery flow: **a)** Reference image; **b)** projection femoral artery velocity at baseline, **c)** post-occlusion hyperemia.

Results: Inter-group comparisons are presented in **Fig. 3**, suggesting deteriorated vascular health in smokers relative to nonsmokers but also in the old relative to young subject group, in terms of vascular reactivity and endothelial function and arterial stiffness. One important finding of the analysis was that the effects of smoking and age were independent of each other, allowing comparison of smokers to nonsmokers (S, NS) and old to young subjects (O, Y) (last two panels in Fig. 3). **Table 1** shows mean difference in parameters evaluated to be less than the coefficients of variation (CV) within non-smoking and smoking groups.
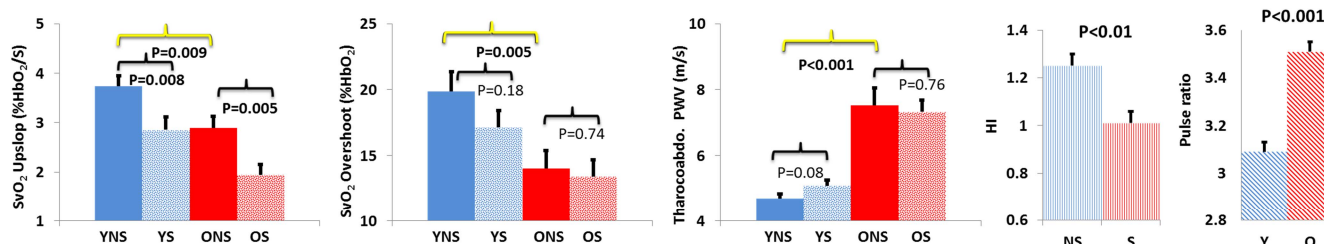

Fig. 3 Comparison of select parameters for endothelial dysfunction and vascular reactivity between subject groups (mean ± SE). For definition of parameters see text and **Fig. 2**. HI=Hyperemic Index= ratio of peak flow/SP; see **Fig. 2b** for definition of SP. Pulse ratio=SP/DP.

Parameter	Avg. abs.% diff.	CV (NS) N=90	CV (S) N=79	ICC
Washout	16	27	40	0.81
Upslope	24	46	63	0.84
Overshoot	24	58	53	0.84
Pulse Ratio (PR)	13	23	22	0.75
Time Forward Flow (T_{ff})	30	44	50	0.71
aPWV	19	24	29	0.66
taPWV	18	36	35	0.80
ifPWV	26	25	31	0.54

Table 1 Results from repeat scans in N=21 subjects in comparison to inter-group differences.

Conclusions: Results indicate MRI biomarkers of EDF to strongly and independently depend on age and smoking history. Measurement repeatability is suggestive of the method's potential to study longitudinal effects in response to life-style changes.

References: [1] Jha et al, NEJM 2013; [2] Langham et al, MRM 2010; [3] Langham and Wehrli, JCMR 2011; [4] Langham et al, JCMR 2013.