

# Probing Myocardial Blood Oxygenation Reserve of Canines with Controlled Hypercapnia Using T2-prepared BOLD MR

Hsin-Jung Yang<sup>1</sup>, Roya Yumul<sup>1</sup>, Richard Tang<sup>1</sup>, Ivan Cokic<sup>1</sup>, Michael Klein<sup>2</sup>, Avinash Kali<sup>1</sup>, Olivia Sobczyk<sup>2</sup>, Behzad Sharif<sup>1</sup>, Jun Tang<sup>1</sup>, Xiaoming Bi<sup>3</sup>, Sotirios

Tsaftaris<sup>4</sup>, Diabao Li<sup>1</sup>, Antonio Conte<sup>1</sup>, Joseph Fisher<sup>2</sup>, and Rohan Dharmakumar<sup>1</sup>

<sup>1</sup>Cedars Sinai Medical Center, Los Angeles, California, United States, <sup>2</sup>University of Toronto, Toronto, ON, Canada, <sup>3</sup>Siemens Medical Solutions, IL, United States,

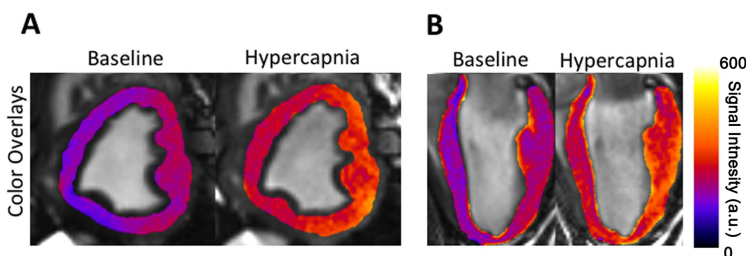
<sup>4</sup>IMT Institute for Advanced Studies Lucca, Lucca, Italy

**Introduction** Cardiac stress testing is the standard of care for diagnosing ischemic heart disease.[1] It is performed in nearly 10 million patients each year in the US alone. It is conventionally initiated with exercise to induce hyperemia and coupled with imaging to identify hypo-perfused myocardial territories. However, about half of the patients find it difficult to exercise to an adequate extent, necessitating intravenous infusion of pharmacological vasodilators, such as adenosine, to simulate the heart's response to exercise. Nonetheless, these drugs carry the potential for side effects and are contraindicated in many patients considered for testing[2]. Arterial partial pressure of CO<sub>2</sub> (PaCO<sub>2</sub>) directly influences coronary blood flow; and modest hypercapnia (10-15 mmHg above baseline) is physiologically benign[3]. However, precise control, modulation and monitoring of PaCO<sub>2</sub>, without altering the arterial partial pressure of O<sub>2</sub> (PaO<sub>2</sub>), in spontaneously breathing humans were not possible until recent development of prospective end-tidal targeting technique[4]. In this abstract, we evaluated the feasibility of a non-invasive and safe stress-testing paradigm using a precisely targeted partial pressure of arterial CO<sub>2</sub> (PaCO<sub>2</sub>) to induce myocardial hyperemia, and compared this response to intravenous adenosine using myocardial blood oxygenation dependent MRI.

**Methods** Canines (n=18) were studied with and without surgically implemented coronary stenosis to examine whether the increase in PaCO<sub>2</sub> (PETCO<sub>2</sub> ~ 35 mmHg to 55 mmHg) can replicate the hyperemic response of intravenous adenosine (140 µg/kg/min). Blood-Oxygen-Level-Dependent (BOLD) CMR was used to determine the effects of hypercapnea. All imaging studies were performed on a 3 T clinical MRI system (Siemens MAGNETOM Verio®, Erlangen, Germany). Following whole-heart shimming and localization of true axes of the heart, ECG-triggered, motion-corrected, free-breathing T2-prepared SSFP acquisitions were prescribed over a mid-ventricular slice along the short-axis at each targeted PaCO<sub>2</sub> level(as described above). Images were acquired with following parameters: single-shot acquisitions with GRAPPA (rate 2) and 4 signal averages; T2-prep time = 40 ms; TR/TE = 2.9/1.5 ms; flip angle = 45°; slice thickness = 6 mm; in-plane resolution = 1.4 x 1.4 mm<sup>2</sup>; and readout bandwidth (BW) = 1371 Hz/pixel. BOLD acquisitions were randomized between adenosine and CO<sub>2</sub> protocols and prescribed over identical imaging slices. In either case, the canines were allowed to recover to baseline conditions between the protocols. In stenosis studies, BOLD acquisitions were repeatedly prescribed as follows: (a) under PETCO<sub>2</sub> ~ 60 mmHg; (b) following recovery to baseline PETCO<sub>2</sub> ~ 40 mmHg, approximately over 5 minutes; and (c) 3 minutes after adenosine infusion (as before).

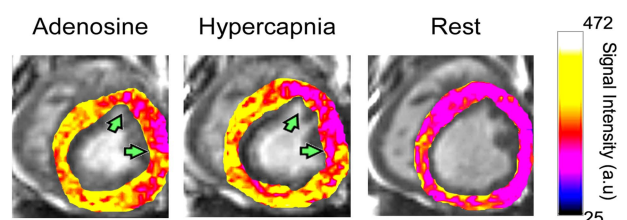
**Results** The hypercapnia-induced hyperemic response in healthy canines was visualized as an increase in BOLD signal intensity relative to baseline (Figure 1). Mean % Hyperemic BOLD Responses between the two hyperemic and baseline states did not differ (p=0.07). Mean % Hyperemic BOLD Responses during peak hypercapnia (mean PETCO<sub>2</sub> = 56±5 mmHg, Table 1) and adenosine infusion were not statistically different (p=0.37). BOLD images from LAD stenosis subjects showed diminished BOLD responses in the Affected (LAD supply territory), but increased (hyperemic) responses in the Remote (unaffected) territory in the presence of hemodynamically significant LAD stenosis (Figure 2). % Hyperemic BOLD Response under hypercapnia (mean PETCO<sub>2</sub> = 55±3 mmHg) and adenosine from the Affected and Remote segments in the presence of hemodynamically significant LAD stenosis showed no difference in the responses to the two vasodilatory stimuli (p=0.12) in canines with patent coronary arteries; there was, however, a significant (p = 0.01) difference in % Hyperemic BOLD Response between Remote and Affected segments in canines with LAD stenosis. The concordance between the segments identified as ischemic with adenosine and hypercapnic stimuli was high (κ=0.75), indicating that the region and extent of ischemic and non-ischemic territories identified with both forms of stimuli are not different.

**Discussion & Conclusion** Our study is the first proof-of-concept study to demonstrate that precisely controlled hypercapnia can induce myocardial hyperemia equivalent to that induced by adenosine infusion under conditions of health and coronary narrowing. Coupled with BOLD CMR, this approach points to a new opportunity for a truly non-invasive cardiac stress test. Nevertheless, human studies are needed to examine the practical utility of this approach in the clinical arena.



**Figure 2** BOLD MR based evaluation of adenosine versus hypercapnia in the presence of LAD stenosis in canines. Representative color-overlaid BOLD CMR images acquired during adenosine infusion, hypercapnia, and rest from a canine with a significant narrowing of LAD is shown. Color bar shows the BOLD MR signal intensity. Images acquired under adenosine infusion and at rest were obtained under normocapnia.

**Figure 1** Effect of changing arterial CO<sub>2</sub> on BOLD CMR signal intensities. Representative short (A) and long (B) axis BOLD CMR images collected from a canine under baseline (PETCO<sub>2</sub> = 42 mmHg) and hypercapnia (PETCO<sub>2</sub> = 55 mmHg) are shown. Note the increase in signal intensity in images under hypercapnia relative to baseline.



Ref:[1] Hachamovitch Circ. 2003.[2] Nakayama J Cardiol. 2009. [3] Spano Rad. 2013 [4] Prisman Int J Radiat Biol. 2007