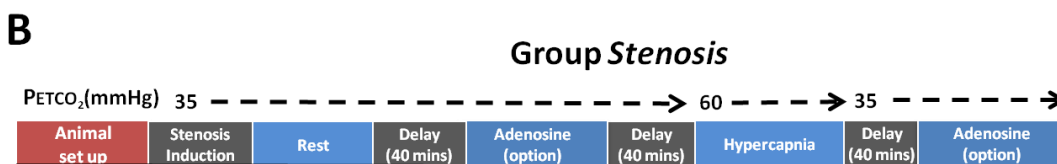
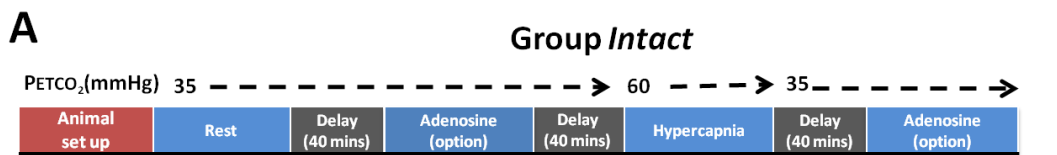
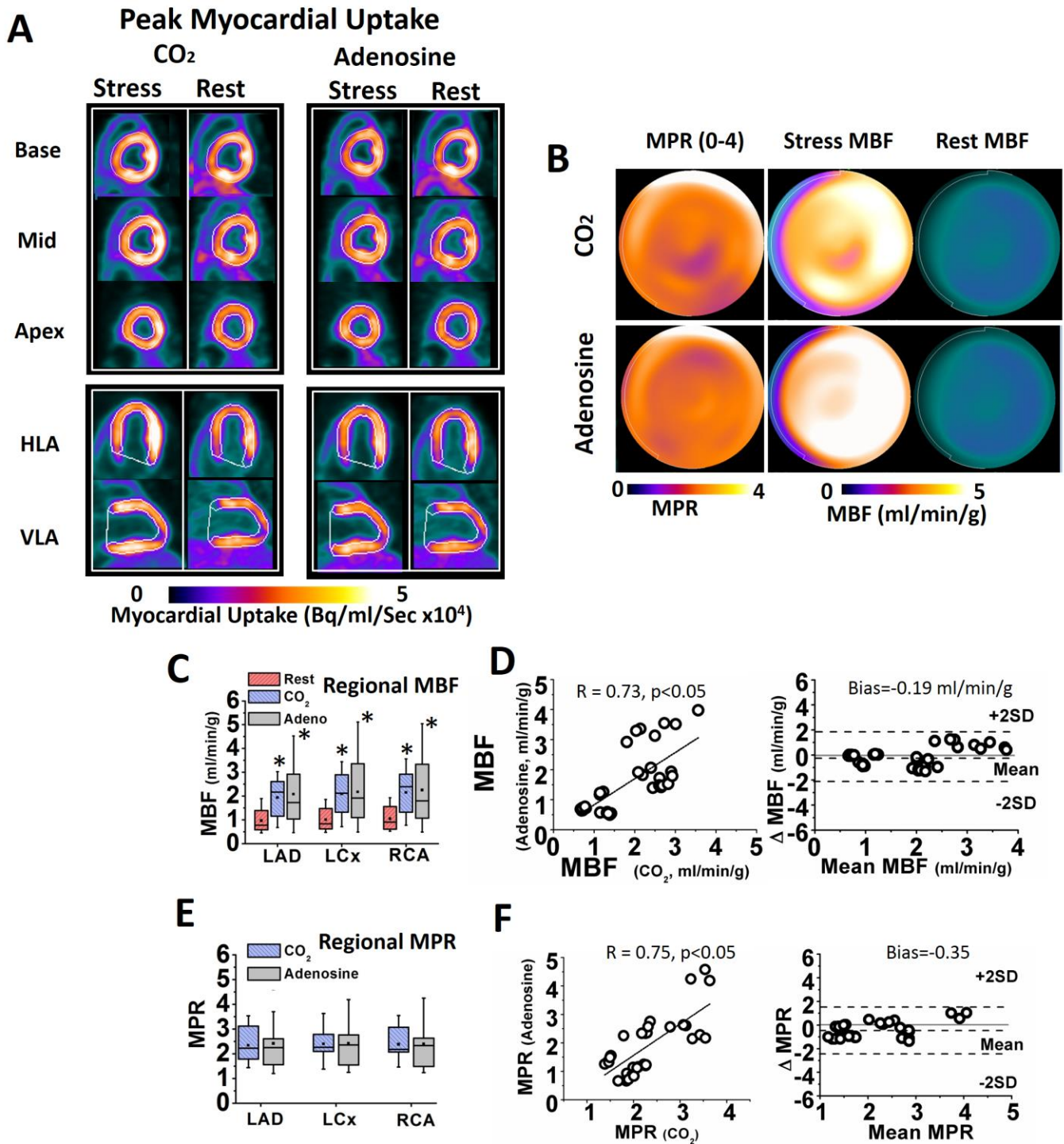


**Supplemental Figure 1** *MRI-based validation of non-flow limiting stenosis.* Balanced steady-state free-precession cine images were acquired in the presence of LAD stenosis at rest. End diastolic and systolic images from the cine series are shown in panels A and B. Note the absence of any wall motion or hyperintense regions (indicative of edema) in the anterior segments of the myocardial wall. Panels C and D show first-pass perfusion images at peak myocardial enhancement and late-gadolinium enhanced images obtained at rest, which show the absence of perfusion defects and infarction, respectively.

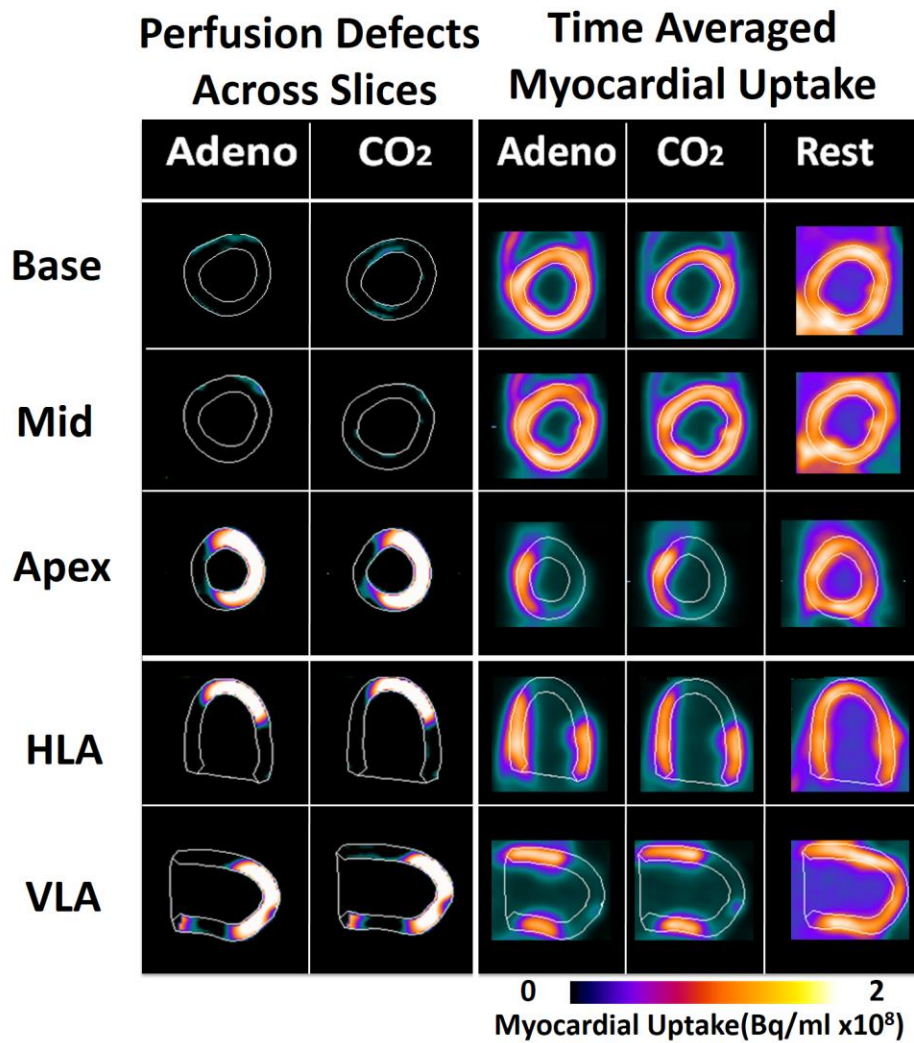


**Supplemental Figure 2** Chronological order of  $^{13}\text{N}$ -ammonia PET data collection in Group intact (A), Group Stenosis (B) and Group Caffeine (C). PETCO<sub>2</sub> at the different points of imaging are shown over the blocks. PETCO<sub>2</sub> was held constant as described in text. In all studies, adenosine and hypercapnia were randomized (“Adenosine (option)” denotes that PET images were acquired before or after hypercapnia, but only once). At least a 50-minute delay was introduced between PET acquisitions to ensure sufficient decay of the radiotracer between acquisitions. In *Group Stenosis*, LAD stenosis was induced as described in text with additional MRI scans performed at the very end (not shown) to ensure absence of rest flow defects, myocardial stunning or infarction. In *Group Caffeine*, pre- and post-caffeine rest exams were performed in the order as described and the PET acquisitions under adenosine and hypercapnia were performed post-caffeine and the order was randomized.



**Supplemental Figure 3** *Global and Regional Myocardial Blood Flow Response to Hypercapnia and Adenosine in Intact Canines.* Panel A shows representative short- (Base, Mid, Apex) and long-axis (horizontal (HLA) and vertical (VLA)) PET images at peak myocardial uptake of <sup>13</sup>N-ammonia during hypercapnia of PaCO<sub>2</sub> ~ 60 mmHg (CO<sub>2</sub>), standard dose of adenosine infusion (Adenosine) and under baseline conditions (PaCO<sub>2</sub> ~ 35 mmHg, Rest). Panel B shows the corresponding Myocardial Perfusion Reserves (MPRs) under hypercapnia and

adenosine as well as myocardial blood flow (MBF) as polar maps. Panel C shows the regional mean MBF at rest and under hypercapnia and adenosine. Panel D shows the correlation (linear regression) and agreement (Bland-Altman plots) between regional MBF under adenosine and hypercapnia. Panel E and F show similar analyses of MPR under hypercapnia and adenosine. \* denotes  $p < 0.05$ .



**Supplemental Figure 4** *Total Myocardial Perfusion Defect Due to Coronary Stenosis Under Hypercapnia and Adenosine.* The figure shows representative short- and long-axis PET images with perfusion defects from the Change Analysis (left) estimated from time-averaged myocardial uptake images (middle) at rest and stress (hypercapnia and adenosine).

Global and regional MBF and MPR values obtained from  $^{13}\text{N}$ -ammonia PET images from the different groups of animals under various physiological statuses are shown in Supplement Table 1 (*Group Intact*), Supplement Table 2 (*Group Stenosis*) and Supplement Table 3 (*Group Caffeine*). The results are shown as mean  $\pm$  SD.

**Supplemental Table 1:** *Global and Regional MBF and MPR in Group Intact*

MBF	Global (ml/min/g)	Regional (ml/min/g)		
		LAD	LCx	RCA
Adenosine	2.2 $\pm$ 1.1	2.1 $\pm$ 0.7	2.2 $\pm$ 0.9	2.2 $\pm$ 0.9
Hypercapnia	2.1 $\pm$ 0.9	1.9 $\pm$ 1.3	2.1 $\pm$ 1.4	2.2 $\pm$ 1.4
Rest	0.9 $\pm$ 0.4	0.9 $\pm$ 0.5	0.9 $\pm$ 0.4	0.9 $\pm$ 0.4
MPR	Global	Regional		
		LAD	LCx	RCA
Adenosine	2.3 $\pm$ 1.0	2.3 $\pm$ 0.9	2.4 $\pm$ 0.9	2.3 $\pm$ 0.9
Hypercapnia	2.6 $\pm$ 0.7	2.6 $\pm$ 0.9	2.6 $\pm$ 1.1	2.6 $\pm$ 0.8

**Supplemental Table 2:** *Global and Regional MBF and MPR in Group Stenosis*

MBF	Regional (ml/min/g)		
	LAD	LCx	RCA
Adenosine	1.4 $\pm$ 0.6	2.3 $\pm$ 1.0	2.7 $\pm$ 1.1
Hypercapnia	1.4 $\pm$ 0.3	2.2 $\pm$ 1.0	2.5 $\pm$ 1.1
Rest	0.6 $\pm$ 0.1	0.5 $\pm$ 0.1	0.6 $\pm$ 0.1
MPR	Regional		
	LAD	LCx	RCA
Adenosine	2.2 $\pm$ 0.6	3.8 $\pm$ 1.4	4.7 $\pm$ 1.4
Hypercapnia	2.1 $\pm$ 0.5	3.8 $\pm$ 1.3	4.2 $\pm$ 1.6

**Supplemental Table 3: Global and Regional MBF and MPR in Group Caffeine**

MBF	Global (ml/min/g)	Regional (ml/min/g)		
		LAD	LCx	RCA
Adenosine	0.6±0.2	0.5±0.1	0.6±0.2	0.6±0.2
Hypercapnia	0.9±0.2	0.8±0.2	0.9±0.3	1.0±0.2
Rest (post treatment)	0.6±0.2	0.5±0.2	0.6±0.3	0.6±0.3
Rest (pre treatment)	0.8±0.4	0.8±0.4	0.8±0.4	0.9±0.4
MPR	Global	Regional		
		LAD	LCx	RCA
Adenosine	1.1±0.6	1.1±0.1	1.1±0.2	1.1±0.1
Hypercapnia	1.8±0.2	1.7±0.6	1.8±0.8	1.8±0.7